Clinical Practice Guidelines

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EASL Clinical Practice Guidelines on vascular diseases of the liver☆

European Association for the Study of the Liver*

Summary

Vascular diseases of the liver include portal vein thrombosis (with or without cirrhosis), portosinusoidal vascular disorder, Budd-Chiari syndrome, sinusoidal obstruction syndrome, non-obstructive sinusoidal dilatation and peliosis, splanchnic artery aneurysms, and hepatic arteriovenous fistulas. Except for portal vein thrombosis in cirrhosis, these are all rare conditions. Since the last Clinical Practice Guidelines were issued by the European Association for the Study of the Liver in 2016, much data has been published on the diagnosis and management – medical and interventional – of patients with vascular liver diseases. Based on a thorough review of the relevant literature, recommendations are provided to address key clinical dilemmas. The document emphasises personalised care, considering individual risk factors and clinical presentation. Multidisciplinary management involving hepatologists, haematologists, pathologists, interventional radiologists and surgeons is essential in this area. Our aim is to provide guidance on the management of patients with vascular liver diseases based on the best available evidence.

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Introduction

Vascular liver diseases encompass a diverse group of conditions affecting the intrahepatic vasculature, as well as the liver inflow (portal vein, splanchnic arteries) and outflow (hepatic veins) systems. These disorders can lead to significant morbidity and mortality, and their management often requires a multidisciplinary approach. These Clinical Practice Guidelines (CPGs) proposed by the European Association for the Study of the Liver (EASL) provide a comprehensive overview of risk factors, diagnosis and management strategies for vascular liver diseases.

Portal vein thrombosis (PVT) is the most common form of splanchnic vein thrombosis. PVT involves the formation of a thrombus in the portal vein or its branches, which can lead to portal hypertension and its associated complications. PVT can occur in patients with or without cirrhosis, with differences in risk factors and management. Budd-Chiari syndrome (BCS) is a rarer condition, occurring at least 10-fold less frequently than PVT.[1,2] BCS is defined as an obstruction of hepatic venous outflow at any level from the small hepatic venules to the junction of the inferior vena cava with the right atrium. Sinusoidal obstruction syndrome (SOS), also known as veno-occlusive disease (VOD), is a potentially life-threatening complication, occurring typically after haematopoietic stem cell transplantation (HSCT). However, it can also occur in other settings, such as after exposure to certain chemotherapeutic agents. Non-obstructive sinusoidal dilatation (NO-SD) is characterised by the dilation of liver sinusoids without significant obstruction of blood flow. It can be associated with various conditions, including drug use, infections, and inflammatory disorders. Splanchnic artery aneurysms (SAA) are aneurysms that occur in the arteries supplying the splanchnic organs, including the liver. These aneurysms can rupture and lead to life-threatening haemorrhage. Endovascular treatment may be necessary to prevent those events, according to the type (true or pseudo-aneurysm), the location, and the size of the aneurysm. Hepatic arteriovenous fistulas are abnormal connections between hepatic arteries and veins. These fistulas can cause portal hypertension and other complications.

Methodology used to develop the present guidelines

The EASL Governing Board initiated these CPGs in October 2022 by selecting a panel of experts and describing the remit of the assignment. The development of these CPGs followed a standard operating procedure set out by EASL[3] and meets the international standards for CPGs set out by the Guidelines

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◦ Clinical Practice Guideline Panel: Chair: Pierre-Emmanuel Rautou; Secretary to the Chair: Lucile Moga; EASL Governing Board representative: Virginia Hernandez-Gea; Panel members: Walter Ageno, Sarwa Darwish Murad, Juan-Carlos Garcia-Pagan, Maria Guido, Valérie McLin, Dhiraj Tripathi, Valérie Vilgrain.

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International Network. The process involves identification of several key questions pertinent to the subject matter. The CPG panel drafted questions according to the PICO format. P – patient, problem, or population, I – intervention, C – comparison, control or comparator, O – outcome. PICO questions were vetted through a simplified Delphi process by a 31-member panel, including clinicians, patients, and other stakeholders competent in the field of vascular liver diseases beyond the CPG panel and the EASL Governing Board. As all the PICO questions reached >75% agreement in the first round of the Delphi process, no second round was needed. A literature search was then performed using PubMed, and expanded to Embase, Google Scholar and Scopus when needed. Each expert took responsibility, made proposals for statements and recommendations for a specific section of the guideline and shared evidence and text with the full panel. The panel met virtually on 12 occasions, and all recommendations were discussed and approved by all participants. The level of evidence was graded according to the Oxford Centre for Evidence-Based Medicine system (Table 1)[4] and the strength of the recommendations was categorised as either 'weak' or 'strong' (Table 2). The higher the quality of the evidence, the more likely a strong recommendation was made. If no clear evidence was available, recommendations were based on the expert opinion of the panel members. All recommendations were subsequently submitted for approval through a second Delphi round. The classification of consensus strength was as follows: Strong consensus if ≥95% agreement, consensus if ≥75% to <95% agreement, majority agreement if ≥50 to <75% agreement, no consensus if <50% agreement. The technical solution has been supported by the Clinical Guideline Service group (https://www.guidelineservices.com), which has provided an online platform, where all CPG documents have been uploaded and reviewed by the Delphi panel. All recommendations and associated text were externally reviewed and ultimately sent to the EASL Governing Board for final approval.

Table 1. Level of evidence based on the Oxford Centre for Evidence-based Medicine.

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomised-controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	RCT or observational studies with dramatic effects; SR of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Non-randomised-controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than an individual study)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

Table 2. Grades of recommendation.

Grade	Wording	Criteria
Strong	Shall, should, is recommended. Shall not, should not, is not recommended.	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested. May not, is not suggested.	

Aetiological factors in primary Budd-Chiari syndrome or portal vein thrombosis without cirrhosis

PVT is more common in males than in females, with a median age at diagnosis of around 55 years, while BCS shows no sex differences and a younger median age at diagnosis of between 35 and 40 years.[1,2,5]

PVT and BCS can be classified as provoked or unprovoked, referring to the presence or absence of local or systemic predisposing factors. The identification of provoking factors has important prognostic implications and drives therapeutic strategies. Even after a careful work-up, in about 15% to 25% of patients, no predisposing factors are actually identified.[6,7] The relative incidence of risk factors varies with age, economic status, geographical area, and site of thrombosis. For example, a local precipitating factor is common in PVT, but not in BCS. As venous thromboembolism is well known as a multifactorial disease, the possibility that multiple concomitant predisposing factors are present should always be considered.

In patients with primary Budd-Chiari syndrome or PVT without cirrhosis, what work-up should be carried out to identify risk factors for thrombosis?

Recommendation

- The presence of local risk factors including solid abdominal cancer and intrabdominal inflammation or infections should be carefully investigated. In the absence of solid cancer, patients should be extensively assessed for the presence of underlying systemic risk factors (Table 3) **(LoE 2, strong recommendation, consensus).**

Abdominal cancer is present in up to 30% of patients with PVT. PVT may be the first manifestation of an occult abdominal cancer, in particular liver or pancreatic cancer, with a higher incidence of newly diagnosed cancer during the first 3 months after PVT diagnosis, while the occurrence of PVT is a negative prognostic marker for survival.[8] Inflammatory or infectious abdominal diseases are reported in 20–30% of patients, and PVT secondary to abdominal surgery occurs in about 10% of cases.[6,9] Conversely, local risk factors are infrequent in patients with BCS (about 5%).[10]

Table 3 summarises all principal risk factors for PVT and BCS and the suggested work-up. This work-up should be initiated rapidly after PVT or BCS diagnosis. The prevalence of these risk factors differs between PVT and BCS, as described elsewhere.[11]

PVT and BCS have also been reported following SARS-CoV-2 infections.[12] Whether SARS-CoV-2 vaccination also favours PVT and BCS is unclear.[13] Cytomegalovirus infection is a risk factor for PVT.[14]

Other diseases that are associated with BCS, albeit rarely, include sarcoidosis, connective tissue disease, and celiac

Table 3. Principal risk factors associated with BCS and PVT.

Risk factor	Major and permanent risk factor	Diagnostic test	When to search	Impact on therapeutic choice	Notes
Solid abdominal cancer: liver, pancreas, colon, bladder, stomach, prostate, breast, and kidney	Yes, while cancer is active	Laboratory testing, CT scan, endoscopy if stomach or colon cancer suspected	Routinely	VKAs are inferior to DOACs and LMWH in this setting. Higher risk of bleeding in gastrointestinal cancer and potential for drug-drug interactions between DOACs and chemotherapy. Consider LMWH in these patients. Consider continuing treatment for as long as the cancer remains active.	Liver and pancreatic cancer are the most common.
Infectious/inflammatory diseases: pancreatitis, cholecystitis, cholangitis, IBD	No	Laboratory tests, CT scan, endoscopy if IBD suspected	Routinely	Consider indefinite treatment duration in active IBD.	Active IBD carries a higher risk of GI bleeding and increased risk of recurrence of PVT or thrombosis in other sites.
Myeloproliferative neoplasms	Yes	Laboratory testing, *JAK2*^{V617F} mutation, next-generation sequencing for other mutations (*JAK2* exon 12, calreticulin, myeloproliferative leukemia virus oncogene), bone marrow biopsy, blood cell mass	JAK2^{V617F} mutation routinely Consider other tests if *JAK2*^{V617F} negative	Risk of bleeding increased, but similar between VKAs and DOACs.	Polycythemia vera is the most common, followed by essential thrombocytopenia. Myelofibrosis rarely involved. *JAK2*^{V617F} mutation may be present even in the absence of other laboratory features.
Other haematological malignancies	Unclear	Laboratory testing, CT scan, bone marrow biopsy	Only when physical examination and general laboratory findings are suggestive	Very limited evidence on efficacy and safety of DOACs, potential for increased risk of bleeding.	Intra-abdominal lymphomas may cause PVT when close to splanchnic veins; acute lymphoblastic leukaemia is associated especially if treated with L-asparaginase in combination with corticosteroids. Multiple myeloma, treated with immunomodulatory agents and with corticosteroids, and acute promyelocytic leukaemia have also been reported to be associated with PVT.
Inherited thrombophilia	Yes for: homozygous factor V Leiden and prothrombin gene mutation or double heterozygosity of the two mutations. Unclear for: protein C, protein S, antithrombin deficiency No for: heterozygous factor V Leiden, prothrombin gene mutation	Factor V Leiden and prothrombin gene mutations. Protein C, protein S, and antithrombin activities	Routinely	Inherited thrombophilia should not drive the choice of the anticoagulant drug but may drive treatment duration (see section dedicated to PVT and BCS). Absence of inherited thrombophilia may support treatment discontinuation in specific cases (see section on chronic PVT).	Diagnosis of antithrombin, protein C and protein S deficiency is possibly hampered by concomitant liver function impairment leading to reduced synthesis of coagulation factors. False positive results may be also caused by testing during the acute phase, during pregnancy or hormonal therapy (protein S in particular), and by concomitant administration of anticoagulant drugs (heparins for antithrombin, VKAs for protein C and S).

(*continued on next page*)

Table 3. (*continued*)

Risk factor	Major and permanent risk factor	Diagnostic test	When to search	Impact on therapeutic choice	Notes
Antiphospholipid antibodies syndrome	Yes	Lupus anticoagulant, anticardiolipin antibodies, and anti-Beta2 glycoprotein 1 antibodies	Routinely	DOACs are not currently recommended in patients with double or triple positive tests Indefinite treatment duration.	Potential interfering with the results of testing for antiphospholipid antibodies may occur during the first 4-6 weeks after BCS or PVT diagnosis, leading to false positive or false negative results. Concomitant use of DOACs may lead to false positive results of lupus anticoagulant test. When positive, lupus anticoagulant, anticardiolipin antibodies, and anti-Beta2 glycoprotein 1 antibodies must be repeated after 12 weeks for confirmation.
Paroxysmal nocturnal haemoglobinuria	Yes	Flow cytometry	Routinely in BCS. In PVT, test in the presence of intravascular haemolysis (*e.g.* haemoglobinuria, high serum LDH concentration) or unexplained cytopenia	Disease specific treatment (*e.g.* eculizumab, ravulizumab) and anticoagulant treatment	Detection of small paroxysmal nocturnal haemoglobinuria clones in PVT or BCS without clinical features has been reported, but clinical significance uncertain.
Behçet's disease	Yes	Clinical features (ocular lesions, genital aphthosis, oral aphthosis, skin lesions, neurological manifestations), pathergy test, HLA B51	History of venous or arterial thrombosis and concomitant disorders including ocular, mucocutaneous, and gastrointestinal manifestations	Glucocorticoids, immunosuppressive therapy, anticoagulant treatment.	Young male patients are more affected by vascular Behçet. Venous thrombosis in up to 40% of cases, including BCS. Anticoagulant treatment alone ineffective without concomitant immunosuppressive treatment.
Oestrogen-derived oral contraceptives and hormonal replacement therapy	No	Medical history	Routinely	Stop oestrogen-derived oral contraceptives and hormonal replacement therapy.	—
Pregnancy	No	β-HCG	Routinely	Please see section dedicated to pregnancy in these guidelines.	—

BCS, Budd-Chiari syndrome; DOACs, direct-acting oral anticoagulants; GI, gastrointestinal; IBD, inflammatory bowel disease; LMWH, low molecular weight heparin; PVT, portal vein thrombosis; VKA, vitamin K antagonists.

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disease. Abdominal obesity has also been found to be more prevalent in patients with PVT who lack other risk factors for thrombosis than in the general population, suggesting it may contribute to PVT development.[15]

Despite careful investigation, no risk factors for thrombosis are identified in 15–25% of patients.[11]

In patients with primary Budd-Chiari syndrome or PVT without cirrhosis, should risk factors for thrombosis influence therapeutic strategies?

Recommendation

- Therapeutic strategies, particularly the selection of different anticoagulant agents, should be based on the underlying risk factors for thrombosis (Table 3). The duration of anticoagulant treatment should consider whether these risk factors are transient or permanent in nature **(LoE 2, strong recommendation, strong consensus).**

Risk factors associated with BCS and PVT not only influence prognosis, but also therapeutic strategies. In particular, risk factors may impact on the selection of the anticoagulant drug, on the need for concomitant treatments, and on the duration of secondary prevention, as described in Table 3.

In patients with PVT or BCS and myeloproliferative neoplasm, cytoreductive drugs may reduce the risk of recurrent thrombosis, but additional evidence is required.[16,17] Target platelet count and haemoglobin concentration for cytoreductive drugs may be lower in patients with signs of portal hypertension than in those without.

In patients with BCS or PVT and some underlying autoimmune diseases, anticoagulant treatment alone may be ineffective. For example, in patients with Behçet's disease, treatment should target inflammation.[18] Immunosuppressant drugs are pivotal for the prevention of recurrences, while the role of anticoagulant therapy remains controversial.[19]

In children with primary Budd-Chiari syndrome or PVT without cirrhosis, should the same diagnostic work-up as in adults be used to identify underlying risk factors?

Recommendation

- The same work-up should be performed in children as in adults, bearing in mind that age-specific cut-offs should be considered for inherited thrombophilia (protein C, protein S, and antithrombin levels). If clinical suspicion persists, testing should be repeated in adolescence **(LoE 4, strong recommendation, consensus).**

As in the adult population, risk factors for BCS or PVT in the paediatric population include local and systemic risk factors. The prevalence of these risk factors differs between BCS and PVT and according to the age of the patients. The most common risk factors for BCS in paediatric patients include anatomical malformations, *JAK2*^{V617F} mutation, and thrombophilia, bearing in mind that age-specific cut-offs should be considered for inherited thrombophilia (protein C, protein S, and antithrombin levels) The prevalence of *JAK2*^{V617F} mutation was found to be higher in adolescents than in children.[20] The most common risk factors in patients with PVT include local risk factors, such as the use of umbilical vein catheters, omphalitis, surgery, abdominal infections, and abdominal cancer. Among cancer types, neuroblastoma, Wilms' tumour, hepatoblastoma, lymphoma, and germ cell tumours have been reported. Among systemic risk factors in patients with PVT, neonatal sepsis, chemotherapy, *JAK2*^{V617F} mutation, and thrombophilia have been reported.[21,22] Of note, fewer unprovoked events are reported in the paediatric population (less than 10%) than in adults.[22]

Primary Budd-Chiari syndrome

Budd-Chiari syndrome (BCS) is defined as a hepatic venous outflow obstruction located at any level from the small hepatic venules to the junction of the inferior vena cava (IVC) with the right atrium, in the absence of SOS, congestive heart failure or pericardial disease.[23] Primary BCS refers to an endoluminal obstruction caused by a thrombosis or a primary disease of the venous wall. This CPG will only discuss primary BCS.

BCS is a rare disease, with an pooled annual incidence of 1 per million inhabitants and a prevalence of 11 per million in a recent meta-analysis[24] including epidemiology data from France,[2] Northern Italy,[23] Sweden,[25] South Korea and Japan.[26] There is no suggestion of a higher incidence of BCS in the Eastern *vs*. Western hemisphere.

BCS has a very heterogenous presentation that can vary from asymptomatic to acute liver failure (ALF), depending on the extent of the thrombosis, the location of the obstruction and the development of venous collaterals. In the largest multicentre prospective study to date, the most common presenting symptom was ascites (83%), followed by hepatomegaly (67%) and abdominal pain (61%),[7] and a minority of patients presented with hepatic encephalopathy (HE) (9%) or variceal bleeding (5%). ALF is rare, as data from the US National Inpatient Sample registry showed that only 6.1% of all BCS discharge diagnoses involved ALF[27] and ALF due to BCS represents only 1% of all ALF Study Group patients.[28] However, ALF carries a very high inpatient mortality (35%-58%)[27,28] and the distinguishing presentation of ALF in BCS, compared to ALF due to other causes, is higher aspartate aminotransferase than alanine aminotransferase (ALT) levels in 95%.[28] At the other end of the spectrum, 15% of patients with BCS are asymptomatic at the time of diagnosis and present with at least one patent hepatic vein, and/or large intra- and extrahepatic collaterals.[29]

In patients with features of acute or chronic liver disease, what imaging modality should be used to establish the diagnosis of Budd-Chiari syndrome?

Recommendations

- In patients with acute or chronic liver disease, Budd-Chiari syndrome should be systematically sought **(LoE 2, strong recommendation, consensus).**

- Doppler ultrasound should be used as the first-line examination to diagnose Budd-Chiari syndrome **(LoE 2, strong recommendation, strong consensus).**

- Contrast-enhanced cross-sectional imaging by CT or MRI is recommended as the next step to confirm the diagnosis and evaluate the feasibility of treatment options **(LoE 2, strong recommendation, strong consensus).**
- In patients suspected of having Budd-Chiari syndrome with patent hepatic veins on imaging, a liver biopsy is recommended to diagnose small hepatic vein Budd-Chiari syndrome **(LoE 3, strong recommendation, consensus).**
- In patients with radiologically confirmed Budd-Chiari syndrome, a liver biopsy is not recommended **(LoE 2, strong recommendation, consensus).**

All patients suspected of acute or chronic liver disease should undergo imaging with complete assessment of all hepatic vessels and the hepatic parenchyma to rule out BCS. The diagnosis is established when there is absence of blood flow or presence of a thrombus within one or more hepatic veins and/or the IVC. In chronic BCS, the hepatic vein may be substituted by a fibrous cord. Other diagnostic clues include hepatomegaly, caudate lobe hypertrophy, a visible caudate vein, heterogeneous liver parenchyma, and intrahepatic veno-venous collaterals. Frequently, specific or non-specific signs of portal hypertension (*i.e.* ascites, splenomegaly, portosystemic collaterals, visible paraumbilical vein) are already present at diagnosis.[30,31]

The choice of imaging modality usually depends on the availability and expertise at the centre. Given the widespread availability and low costs, Doppler ultrasound is usually the first imaging modality used. A recent meta-analysis pooling 11 studies showed that Doppler ultrasound has good diagnostic sensitivity (0.89) with reasonable specificity (0.68) and is therefore an excellent first-line examination.[32] However, operator dependency is an important limitation. Contrast-enhanced cross-sectional imaging by CT or MRI is usually the next step to confirm the diagnosis and assess for signs of portal hypertension. CT has an excellent sensitivity (0.89) and good specificity (0.72), while MRI has the highest sensitivity (0.93) but lower specificity (0.55).[32] Hepatic venography is recommended when the diagnosis remains uncertain. In patients with typical BCS symptoms (ascites, hepatomegaly, abdominal discomfort), but patent hepatic veins and IVC on imaging, it is important to perform a liver biopsy to rule out small vein BCS, a rare variant in which the obstruction is confined to the hepatic venules.[33] In all other cases, a liver biopsy is not needed for the diagnosis of BCS.

In patients with primary Budd-Chiari syndrome, what management strategy should be followed to reduce morbidity and mortality?

Recommendations

- In patients with primary, non-fulminant, Budd-Chiari syndrome, a stepwise management strategy should be followed consisting of anticoagulation and treatment of underlying conditions, followed consecutively by percutaneous angioplasty, TIPS, and LT in non-responsive patients **(LoE 2, strong recommendation, strong consensus).**
- Patients with Budd-Chiari syndrome should therefore be treated in collaboration with centres with expertise in vascular liver diseases and LT **(LoE 5, strong recommendation, strong consensus).**
- Therapeutic anticoagulation should be initiated as soon as possible after diagnosis and continued indefinitely, unless contraindicated **(LoE 2, strong recommendation, strong consensus).**
- Low-molecular-weight heparin followed by vitamin K antagonists is the recommended anticoagulation therapy **(LoE 3, strong recommendation, consensus).**
- Unfractionated heparin should be avoided due to the risk of heparin-induced thrombocytopenia **(LoE 3, strong recommendation, strong consensus).**
- Direct oral anticoagulants may be considered in patients with preserved liver function **(LoE 4, weak recommendation, consensus).**
- Proper variceal prophylaxis should be ensured to avoid bleeding, but it should not delay initiation of anticoagulation **(LoE 3, strong recommendation, consensus).**
- In patients with short-segment stenoses in the inferior vena cava or hepatic veins, percutaneous transluminal balloon angioplasty should be considered **(LoE 3, strong recommendation, strong consensus).**
- In cases where medical management alone is insufficient to alleviate symptoms and percutaneous transluminal balloon angioplasty is not an option or has failed, TIPS is the recommended next step **(LoE 3, strong recommendation, strong consensus).**
- In patients with acute liver failure, emergency TIPS should be attempted, while in parallel listing the patient for LT, although transplantation may not always be needed **(LoE 3, strong recommendation, strong consensus).**
- In patients with liver disease not responding to medical or interventional therapy or in those with HCC, LT should be considered **(LoE 3, strong recommendation, strong consensus).**

Because of the heterogeneous presentation and variable severity at diagnosis, there is no one-size-fits-all therapy for BCS. The available evidence supports a stepwise strategy.[34,35] This applies to all patients except those who present with ALF, in whom liver transplantation (LT) should be considered from the start. In the largest published series, such a stepwise approach resulted in excellent long-term survival, with reported 1-, 3- and 5-year survival rates ranging from 88-96%, 79-89% and 74-89%, respectively.[34,35]

The universal first step is to initiate anticoagulation as soon as possible and continue this indefinitely unless there is a major contraindication. In the prospective series including 157 unselected patients with incident BCS from 9 European countries, 44% of patients were managed by anticoagulation alone, of whom 71% survived.[35] The recommended approach is to start with a therapeutic dose of low-molecular-weight

heparin (LWMH) followed by vitamin K antagonists (VKAs), targeting an international normalised ratio (INR) of 2.0-3.0. The use of unfractionated heparin should be restricted only to situations in which there are contraindications to LWMH, due to the unusually high rate of heparin-induced thrombocytopenia (15-28%) reported in several series[34,36] and to the inherent delay in achieving a stable activated partial thromboplastin time in the therapeutic range. It is important to note that major bleeding after anticoagulation therapy is not uncommon (22.8 per 100 patient-years in a French reference centre).[37] Bleeding originates most often from oesophageal varices but also occurs after invasive interventions (including therapeutic paracentesis) or in the setting of supratherapeutic anticoagulation. Ensuring proper variceal prophylaxis while initiating anticoagulation is of high importance, as detailed in the section "Issues common to vascular liver diseases" below. The experience with off-label use of direct-acting oral anticoagulants (DOACs) in BCS is increasing and preliminary data from a few case series suggest that DOACs have comparable safety and efficacy to VKAs.[38,39] However more data is needed before DOACs can be recommended in all patients.

Besides anticoagulation, medical management is directed towards treatment of ascites, HE and varices, in line with the EASL[40–42] and Baveno VII[40] recommendations for the treatment of these conditions in cirrhosis.

The next step in management is to actively look for short-segment stenoses in the IVC or hepatic veins that could be amenable to percutaneous transluminal balloon angioplasty and/or stenting, regardless of the response to anticoagulation. Technical success rates are high in experienced centres, but primary patency is low (58%) and reinterventions are needed in two-thirds of patients. Secondary patency after reintervention is however excellent, especially when combined with stenting.[43–45] Catheter delivered thrombolysis can be useful as adjunctive therapy to improve initial recanalisation or treat immediate rethrombosis during the percutaneous transluminal balloon angioplasty procedure.[46] However, there is no role for systemic or local thrombolysis as a standalone therapy, given its low success rate and the high rate of major bleeding complications.[46,47]

In two-thirds of cases, medical management alone is insufficient to alleviate symptoms and/or percutaneous transluminal balloon angioplasty is not an option or has failed. In this setting, portosystemic shunting, in particular TIPS, is the next step. Given the now widespread availability and experience with TIPS, and the high shunt dysfunction rate and mortality[48] of surgical shunting, the latter has now become obsolete. However, TIPS placement in BCS is technically challenging and should be restricted to experienced referral centres. The shunt is created either through the hepatic vein stump or directly by the transcaval approach (*i.e.* direct intrahepatic portosystemic shunt).[49] Technical success rates in experienced hands are high (93-98%);[49–51] however, TIPS dysfunction remains common (24-44%) despite the use of covered stents.[49,51–53] Secondary patency rates approach 98%,[51,52] as most dysfunctions can be repeatedly treated by angioplasty and/or additional stenting, as long as there is close follow-up after TIPS. Bare stents have significantly higher dysfunction rates (72%-88%) and should generally be avoided in BCS. HE occurs after TIPS in 21% of cases[49,52] and is managed medically as in cirrhosis, although in some cases refractory HE becomes an indication for LT.[49] LT-free survival after TIPS placement was 77-88% and 64-78%, at 1 and 5 years, respectively, in two European multicentre studies.[35,49]

LT is needed in 13-18% of patients.[34,35] Indications include fulminant hepatic failure (12-21%), development of hepatocellular carcinoma (HCC) (1-10%) and progressive liver disease not responding to medical or interventional therapy.[54–56] There is no clear definition of fulminant hepatic failure or universal criteria for high urgency listing in the setting of acute BCS. Current outcomes following LT for BCS are generally favourable, with European Liver Transplant Registry and single-centre studies reporting 1- and 10 year patient survival rates of between 76-92% and 68-84% and graft survival rates of 88-92% and 68%-72%, respectively.[54,56–60] Compared to patients undergoing elective LT, those who undergo high urgency listing have a significantly lower 3-month survival rate, but similar outcomes thereafter.[55] Pre-transplant TIPS does not preclude transplantation nor impact post-LT outcomes[60] and can be lifesaving (salvage procedure) while waiting for an organ. Long-term outcomes after LT are similar for patients with underlying myeloproliferative neoplasm[60–62] and there is no evidence of expedited malignant transformation on immunosuppression. However, there appears to be an increased tendency for thrombotic complications (PVT, hepatic artery thrombosis, venous thromboembolisms, and recurrent BCS)[54,59,63] accounting for some of the graft losses post-LT. This stresses the need for ongoing anticoagulation after transplantation. While in deceased donor LT, the recipient IVC can be resected and replaced with the donor IVC, this is not possible in living donor LT. Therefore, living donor LT is technically more challenging in BCS but remains feasible in experienced centres who employ advanced vascular reconstruction techniques.[63–65]

In patients with primary Budd-Chiari syndrome, should prognostic scores be used to guide individual patient management?

Recommendation

- The currently available prognostic scores should not determine individual patient management alone but can be used for research purposes (**LoE 3, strong recommendation, consensus**).

Several prognostic indices (PI) have been developed over the years in order to predict prognosis in patients with BCS: the Clichy PI,[66] the New Clichy PI,[67] the Rotterdam BCS index,[68] the BCS-TIPS PI,[49] and the BCS-ALF score.[27] The model for end-stage liver disease (MELD) was also tested in BCS.[69] Rautou *et al.* investigated the prognostic performance of all the above scores for the prediction of LT or death (best AUC 0.693 for MELD) and intervention or death (best AUC 0.796 for Rotterdam BCS index) in an independent single-centre cohort of 96 patients. They concluded that none of the scores or PI's performed above the threshold required to be useful for individual patient management (*i.e.* AUC >0.80).[70] Moreover, the proportion of variance explained by the PI 's was 37% at best, again too low for individual prediction (requires >50%).

There is however a clear need for an accurate prognostic score that can guide individual management in BCS. Ideally,

this score should 1) be derived from a large cohort of patients treated with contemporary therapies; 2) include variables which are easy to obtain at time of diagnosis; 3) predict solid endpoints (such as death and/or LT); 4) predict short-term outcomes, preferably within 1 year because most events occur within that timeframe and predictions further out are hampered by bias and intercurrent events; 5) exhibit either a continuous or incremental relation with the outcome; 6) be externally validated in several independent cohorts with reasonable sensitivity, specificity and AUC >0.80; and 7) be responsible for predicting over 50% of the variance between patients. Until such a score is developed, the current PIs are insufficient to guiding individual patient management and should be used for research purposes only (*e.g.* adjusting for the severity of liver disease in studies on BCS).

In patients with primary Budd-Chiari syndrome, how should HCC surveillance be performed?

Recommendations

- In patients with chronic Budd-Chiari syndrome, surveillance for HCC should include imaging and AFP measurement every 6 months (Fig. 1) **(LoE 3, strong recommendation, strong consensus).**
- An AFP level of >15 ng/ml should raise suspicion for HCC **(LoE 3, strong recommendation, strong consensus).**
- MRI, preferably with hepatobiliary contrast agents, is recommended to differentiate between benign (hyperintense on T1, hypo/isointense on T2, hyperintense on hepatobiliary contrast sequences) and malignant (hypointense on T1, hyperintense on T2, hypointense on hepatobiliary contrast sequences) lesions **(LoE 3, strong recommendation, strong consensus).**
- For lesions suspected of being HCC, histological confirmation should be obtained **(LoE 3, strong recommendation, consensus).**

In patients with BCS, regenerative liver nodules are known to develop during follow-up. The precise prevalence is not well studied, but a French group recently published a series of imaging studies in which benign nodules were found in 27-50% of cases.[71–73] These BCS nodules resemble focal nodular hyperplasia (FNH) and are therefore often called FNH-like lesions.[74] These FNH-like lesions are typically numerous and variable in size. They most often occur in the right liver lobe,[75] can display a central scar, have not been described in cases of (sub)acute BCS and may show significant changes over time. Other benign liver lesions, in particular hepatocellular adenomas, can also occur in BCS but are relatively rare.[76]

The exact annual incidence of HCC in BCS is lacking. However, cohort data from France,[75] Sweden[77] and South Korea[78] estimate an annual HCC incidence of 0.8-2.8% which appears to increase over time, with a 5-year cumulative incidence of between 3.1-18.5%.

There is currently no evidence for malignant transformation of benign FNH-like lesions into HCC. However, both types of lesions can co-exist, and differentiation between benign and malignant lesions is imperative, but challenging. Clinically, HCC occurs more often in older patients[73] and those with cirrhosis, and is more often larger[72] and/or solitary[75] compared to benign nodules. Also, compared to hepatitis B-related HCC, HCC in BCS is more often well differentiated.[79]

Pathognomonic imaging criteria for HCC *vs*. FNH-like lesions in BCS are lacking. It was recently shown that characteristic hallmark signs of HCC in cirrhosis, *i.e.* arterial phase hyper-enhancement and washout in the portal and delayed phase on either CT or MRI, cannot be extrapolated to patients with BCS.[80] However, there are differences that can be used. On MRI, most HCC nodules appear hypointense on T1 (67%) and hyperintense on T2 (77%), while the majority of benign lesions appear hyperintense on T1 (93%) and hypointense on T2 (81%). Moreover, an alpha-fetoprotein (AFP) level of greater than 15 ng/ml exhibits an excellent positive (100%) and negative (90%) predictive value for the diagnosis of HCC.[75] Acceptable sensitivity and specificity was found for the combination of arterial hyperenhancement + washout and either AFP >15 ng/ml or hypointensity on T1[80]. Recent data suggest that the diagnostic performance of MRI can be further improved by the addition of specific hepatobiliary contrast agents.[72] On hepatobiliary acquisitions, all HCC nodules appeared hypointense (100%) *vs*. only 2% of benign lesions (which all corresponded to hepatocellular adenomas). Combining hypointensity on hepatobiliary contrast MRI with AFP >15 ng/ml rendered an excellent sensitivity of 92% and specificity of 98%.

According to current practice guidelines, surveillance of HCC in cirrhosis of any cause is considered cost effective at an annual HCC incidence of 1.5% or greater.[81] Hence, surveillance for HCC appears justified in BCS. Solid data regarding the optimal frequency or modality for surveillance in BCS are lacking and at the present time, no firm evidence-based recommendations can be made. However, until further data become available, it seems justified to recommend the following practical approach to HCC surveillance in chronic BCS: 6-monthly surveillance with ultrasound and AFP (Fig. 1). In case of focal nodule(s) on ultrasound and/or AFP >15 ng/ml, MRI with hepatobiliary contrast helps characterise nodules. In the case of suspicion of HCC, histological confirmation is needed.

In patients with primary Budd-Chiari syndrome and HCC, should the strategy to treat HCC be different from patients with other chronic liver diseases?

Recommendation

- There is currently no solid evidence to recommend a treatment strategy different from that proposed for patients with other chronic liver diseases. All available treatment options for HCC, including LT, should be considered on a case-by-case basis **(LoE 4, strong recommendation, strong consensus).**

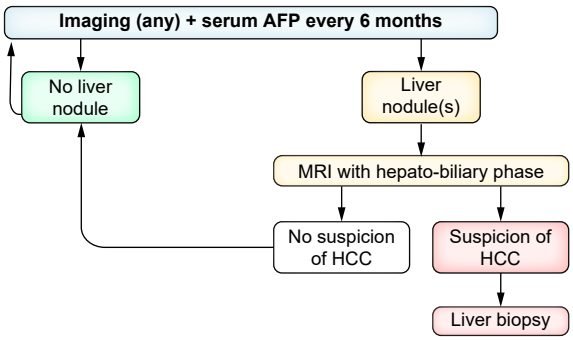

Fig. 1. HCC surveillance modalities in patients with primary Budd-Chiari syndrome. AFP, alpha-foetoprotein; HCC, hepatocellular carcinoma.

The available therapeutic options for HCC in BCS are similar to those for HCC in other chronic liver diseases and include surgical resection, local ablative therapies, transarterial chemo-embolisation (TACE), LT, and probably selective internal radiation therapy. However, data regarding the efficacy or safety of each of these modalities in the setting of BCS are very scarce and come from small case series, mostly in Asia. Only one paper evaluated the efficacy of surgical resection in 38 Chinese patients with BCS, and found that resection with simultaneous venous outflow relief (by cavo-atrial shunt in 22 patients) is associated with improved median survival of 110 months *vs.* 49 months (hazard ratio [HR] 2.4) and less postoperative liver failure and variceal bleeding (9.1% *vs.* 37.1%), less intraoperative blood loss, and shorter duration of surgery *vs.* resection without outflow relief.[82] For reasons that remain unclear, TACE is the most frequently employed treatment for BCS-HCC in Asian reports followed by ultrasound-guided microwave ablation ([83–85]). However, in these papers, details regarding the rationale for using TACE or ablation rather than other modalities are not given, hence it is difficult to draw conclusions from these small series.

In the Western world, HCC was the indication for LT in 10% of patients transplanted for BCS.[56] In a paper using United Network of Organ Sharing data, the majority of patients who underwent LT for HCC had a single tumour (72%) with a mean size of 2.3 cm, located in the right lobe (87.5%) and were treated with locoregional therapy (59%) on the waiting list. Interestingly, HCC did not significantly impact post-LT survival, suggesting that LT is a good treatment option for HCC when transplant criteria are met. However, specific data on HCC recurrence after LT are lacking.

Given these very limited experiences, there is little data to suggest a different treatment strategy for HCC in BCS compared to HCC in other chronic liver diseases. We suggest evaluating each treatment option on a case-by-case basis, taking into consideration tumour size, number and liver function, according to the current EASL guidelines for the treatment of HCC.[81]

In children with primary Budd-Chiari syndrome, should management be the same as in adults?

Recommendation

- Endovascular management is suggested as the first-line therapy in children, combined with post-procedure anticoagulation to prevent recurrence. LT can be considered when endovascular management is not possible or fails **(LoE 5, weak recommendation, consensus).**

Very little data are available to guide the management of BCS in children. One older study recommended prompt surgical mesenteric- or portal-to caval bypass.[86] There are several case reports of successful TIPS for this indication in children from 7 years of age.[87–89] More recently, in a report of 44 children with BCS, half underwent successful interventional angioplasty of whom one-quarter experienced recurrence. The other 50% of patients were managed medically without anticoagulation, but the outcome is not reported as most of these patients were lost to follow-up.[90] Balloon angioplasty may be used as early as 3 years of age and probably sooner.[91] A recent systematic review of children aged 12 months to 18 years analysed the management of 175 patients with BCS. Half of patients on heparin- or VKA-based anticoagulation experienced vessel recanalisation; the numbers were insufficient to draw conclusions regarding radiological treatment.[22]

General considerations in portal vein thrombosis without or with cirrhosis

Recent portal vein thrombosis (PVT) refers to the fresh formation of a thrombus within the portal vein and/or right or left branches that can extend into the mesenteric or splenic veins.

Chronic PVT is defined as a PVT that is present for >6 months.[40] Portal cavernoma corresponds to porto-portal collaterals that may develop following recent PVT.

Thrombosis can occur in patients with or without previous liver disease and can completely or partially occlude the vessel. When PVT extends to the mesenteric vein, it may cause acute abdominal pain[92] as a manifestation of intestinal ischaemia/infarction, which is the most feared immediate complication of recent PVT. Patients, however, may be asymptomatic or present with non-specific symptoms and be diagnosed incidentally by a scheduled imaging study performed for another reason.

In patients with PVT, which standardised definition and classification should be used?

Recommendation

- In patients with or without cirrhosis with PVT, a standardised description of initial site, extent, percent occlusion of main portal vein lumen, and time course (Table 4) is required to assess evolution (**LoE 5, strong recommendation, strong consensus**).

Terminology and classifications of PVT vary broadly in the literature. The Yerdel classification (Table S1) is widely used and its main utility is in guiding surgical strategies at LT and predicting post-transplant outcomes based on thrombosis load and extension beyond the portal vein.[93] However, limitations include the lack of differentiation between recent and chronic PVT, and the absence of other characteristics such as cavernoma and response to treatment or interval change.

A standardised nomenclature has been proposed to homogenise management of patients and facilitate future large studies.[94] We recommend using the same classification as proposed in the American Association for the Study of Liver Diseases 2020 CPG[95] and Baveno VII recommendations,[40] outside the transplantation setting, and the Vascular Liver Disease Interest Group (VALDIG) PVT criteria to assess PVT evolution over time[94] (Table 4).

In patients with recent or chronic PVT/portal cavernoma, what work-up should be performed to search for underlying chronic liver disease?

Recommendations

- A complete clinical evaluation should be performed including searching for risk factors for cirrhosis and conditions associated with PSVD (Table 5), liver blood tests, evaluation of liver morphology using imaging, and LSM **(LoE 5, strong recommendation, consensus).**
- A liver biopsy should be considered to rule out cirrhosis or PSVD in the presence of at least one of the following features: a condition strongly associated with the presence of cirrhosis or PSVD, persistent liver blood test abnormalities, abnormal liver morphology on imaging, or elevated LSM **(LoE 5, strong recommendation, consensus).**

The presence of an underlying chronic liver disease has a major impact on the management of patients developing PVT. Contrary to patients with a healthy liver, patients with cirrhosis usually have portal hypertension as a consequence of PVT development and, although they may achieve recanalisation, portal hypertension will remain. In addition, cirrhosis by itself is a prothrombotic condition that facilitates PVT development and, when present, it is not necessary to search for a specific thrombophilic disorder.[96]

Usually, clinical, morphological and elastography data easily identify underlying cirrhosis. Normal morphology and a smooth surface of the liver suggest that PVT is occurring in a patient with a healthy liver. However, recent PVT may occur in patients with a history of paucisymptomatic or asymptomatic thrombosis, causing atrophy of the ischaemic segments with compensatory hypertrophy of the non-ischaemic segments. This can lead to morphological liver changes that, in some cases, resemble those seen on imaging in patients with chronic liver disease such as cirrhosis. Patients with porto-sinusoidal vascular disorder (PSVD) are at a high risk of developing PVT, which may occur even in the early stages of the disease when they exhibit only minor morphological changes that can be misdiagnosed as

Table 4. Standardised nomenclature for the characterisation of PVT and portal cavernoma.

Feature	Definition		
Time course			
Recent	PVT presumed to be present for <6 months		
Chronic	PVT present or persistent for >6 months		
Percent occlusion of main portal vein			
Minimally occlusive	Clot obstructing <50% of original vessel lumen		
Partially occlusive	Clot obstructing >50% of original vessel lumen		
Completely occlusive	No persistent lumen		
Cavernous transformation	Gross porto-portal collaterals without original PV seen		
Response to treatment or interval change			
Main portal vein thrombus	**Thrombus of the upstream and downstream veins***	**New thrombus site**	**Overall assessment**
Complete resolution†	Complete resolution†	No	Complete resolution
Complete resolution†	No complete resolution or no unequivocal progression‡	No	Improvement
Complete occlusion that becomes partial; increase by >25% of the %RL	Complete resolution; no unequivocal progression	No	Improvement
Increase or decrease of ≤25% of the %RL	No complete resolution or no unequivocal progression‡	No	Stability
Partial occlusion becoming complete; decrease by >25% of the %RL	Any	Any	Progression
Any	Unequivocal progression of one or more thrombosis site	Any	Progression
Any	Any	Yes	Progression

%RL, percentage of the remnant lumen; PV, portal vein; PVT, portal vein thrombosis.
Classification of time course and extension is based on AASLD 2020 Practice Guidance[95] and Baveno VII conference,[40] and PVT evolution on VALDIG PVT criteria.[94]
Regarding response to treatment or interval change, the proposed criteria follow the structure of the RECIST criteria used in oncology.[456] The core concepts are: to assess the thrombus of the main portal vein following the methodology presented; to assess the thrombus of the upstream and downstream veins following the methodology presented above; to assess the occurrence of new thrombus in veins initially free from thrombus; and to combine the above assessments in order to categorise the patients into four categories: complete resolution, improvement, stability, and progression of the thrombus.[94]
*Upstream veins refer to splenic vein, superior mesenteric vein, and inferior mesenteric vein. Downstream vein refers to right and left portal branches.
†Complete disappearance of any thrombus in the considered vein. Synonym of complete recanalisation.
‡Unequivocal decrease of the remnant lumen in the considered vein. This feature is visually assessed. Equivocal progressions should be considered as non-progression.

a healthy liver.[97,98] Then, although imaging studies are extremely helpful, they may not be enough to discard or confirm the presence of an underlying liver disease. Liver stiffness measurement (LSM) helps in equivocal cases. A value below 10 kPa is very rarely associated with the presence of cirrhosis.[99,100] Therefore, a finding of such a low LSM value, despite morphological changes on imaging studies suggesting underlying chronic liver disease, should prompt further investigations.[101] The same applies if hepatic venous pressure gradient (HVPG) is measured and a normal or a mildly elevated value (<10 mmHg) is found.[101] In this setting, a liver biopsy can be used to diagnose an underlying chronic liver disease, including a PSVD, but also rule out any liver lesions.[102]

Therefore, a liver biopsy should be performed to rule out cirrhosis in case of: (i) persistently abnormal liver blood tests; (ii) abnormal morphology of the liver on imaging not typical of chronic PVT without cirrhosis (liver changes seen in chronic PVT without cirrhosis include atrophy of the left lobe, hypertrophy of the caudate lobe and segment IV, and a smooth liver surface);[103] and (iii) a LSM >10 kPa.[104,105] Underlying PSVD can also be suspected, since PVT occurs in about 30% of patients with PSVD.[106,107]

In patients with recent or chronic PVT/portal cavernoma without known cirrhosis, does liver biopsy have an impact on patient management?

Statement

- In patients with recent or chronic PVT/portal cavernoma without known cirrhosis, a liver biopsy has an impact on patient management: (i) when it shows cirrhosis, because screening for liver cancer is indicated; and (ii) when it shows PSVD or cirrhosis in the setting of portal vein recanalisation because both may favour placing a TIPS at the same time as recanalising the portal vein **(LoE 3, consensus).**

Recommendation

- In patients with chronic PVT/portal cavernoma without known cirrhosis, a liver biopsy should be performed: (i) to rule out underlying liver disease when there are unexplained persistently abnormal liver blood tests, liver morphology suggestive of cirrhosis, or elevated LSM; and (ii) prior to portal vein recanalisation **(LoE 5, strong recommendation, consensus).**

In equivocal cases, liver biopsy is the only method that can exclude the presence of cirrhosis and other chronic liver disorders, such as PSVD. Recognising whether a patient with PVT has underlying chronic liver disease can have a major impact on management in the acute setting, but also in the long term. First, diagnosis of cirrhosis implies screening for liver cancer. Second, in the setting of portal vein recanalisation, the presence of PSVD or cirrhosis is an argument in favour of placing a TIPS in order to prevent re-thrombosis.

Recent portal vein thrombosis without cirrhosis

In patients with recent PVT without cirrhosis, are contrast-enhanced CT or contrast-enhanced MRI better than ultrasound techniques with or without contrast agent to diagnose and characterise PVT?

Recommendations

- Ultrasound with or without contrast agent is as good as contrast-enhanced CT or contrast-enhanced MRI to diagnose recent PVT **(LoE 5, strong recommendation, consensus).**

- Contrast-enhanced CT or contrast-enhanced MRI should be used to characterise the extension of PVT (vessels affected and degree of occlusion of the lumen) as they perform better than ultrasound with or without contrast agent **(LoE 5, strong recommendation, strong consensus).**

- Contrast-enhanced CT should be used to characterise possible signs of intestinal ischaemia, as it performs better than other imaging techniques **(LoE 5, strong recommendation, strong consensus).**

Doppler ultrasound is usually the first imaging study to identify PVT. Since a visible hyperechoic thrombus within the portal vein lumen may be absent, Doppler assessment is essential to evaluate blood flow and exclude thrombosis.[108]

Diagnosis of portal venous obstruction should be confirmed by contrast-enhanced CT and/or MR. CT typically shows a hyperattenuating thrombus on the unenhanced phase and an absence of enhancement of the lumen in the contrast-enhanced portal venous phase. Enlargement of the portal vein can be observed when PVT is complete and recent. Although CT and MRI have a higher sensitivity than Doppler ultrasound, there is a risk of false positive results, due to inadequate timing of the contrast phase.[108] A CT scan can provide additional information on: (i) PVT extension; (ii) the presence of a local factor; and (iii) signs of intestinal injury, namely intestinal wall thickening, decreased or absent contrast enhancement, bowel dilatation, pneumatosis intestinalis, or portal venous gas.[109]

In patients with recent PVT without cirrhosis, when should anticoagulation be initiated and for how long should it be continued to optimise outcomes?

Recommendations

- Anticoagulation should be initiated as soon as possible, since early initiation of anticoagulation may reduce the risk of developing intestinal ischaemia and increases the probability of portal vein recanalisation **(LoE 4, strong recommendation, strong consensus).**

- Anticoagulation should be continued for at least 6 months (see "In which patients with chronic PVT/portal cavernoma without cirrhosis, is anticoagulation recommended to prevent thrombotic events?") **(LoE 4, strong recommendation, strong consensus).**

In patients with recent PVT, there are two main goals of anticoagulant treatment: (i) to prevent bowel necrosis requiring bowel resection and (ii) to achieve sufficient recanalisation of the portal venous system to prevent the future development of portal hypertension and its complications.

In a retrospective study, recanalisation was observed in 62% of patients initiating anticoagulation within 1 week of symptoms, but in less than 20% of those initiating anticoagulation after 1 week.[110] In a prospective study of 95 patients with recent PVT and normal liver systematically treated with anticoagulants, the relationship between delay of initiation in anticoagulation and rate of recanalisation was not found. Median time from symptoms (>90% of patients had abdominal pain) to start of anticoagulation was 13 days (range 0-140 days). In this series, only two patients (2%) required limited bowel resection.[92] Conversely, in the absence of anticoagulants, 30% of the patients developed intestinal infarction.[111]

Altogether, in patients with recent PVT, if there are no formal contraindications it is currently recommended to initiate anticoagulation as soon as possible. Ideally, workup for thrombosis risk factors (see above) should be initiated before anticoagulation is started (because anticoagulants interfere with some tests), but this should not delay the commencement of anticoagulation.

The types of anticoagulant are discussed below, in the section "Issues common to vascular liver diseases".

In patients with recent PVT without cirrhosis, regardless of bowel ischaemia, is there an indication for endovascular interventions to reduce morbidity and mortality?

Recommendation

- Anticoagulation, initiated as soon as possible, is the treatment of choice. If there are signs of intestinal ischaemia and no early improvement with anticoagulation, thrombolysis and/or endovascular interventions should be considered in expert centres, while being evaluated by surgeons for potential surgical resection (**LoE 5, strong recommendation, strong consensus**).

Anticoagulation initiated as soon as possible is the first-line therapy for recent PVT in the absence of cirrhosis. In the previously mentioned European prospective study, recanalisation of the portal, splenic and superior mesenteric veins (SMV) was obtained in 39%, 80%, and 73% of anticoagulated patients, respectively.[92] Splenic vein obstruction and ascites (even only on radiology) were associated with the absence of recanalisation.[92]

It should be noted that anticoagulation does not always reverse signs of intestinal ischaemia and that other therapeutic strategies, such as chemical and/or mechanical thrombolysis with or without TIPS may be required.[112] The reported recanalisation rates using thrombolysis, either systemic or local, mechanical and/or chemical, have been shown to be similar to those achieved with anticoagulation alone, but with more common and severe side effects.[47,113,114] A more recent comparison of two cohorts of patients with recent PVT, one treated with anticoagulation and the other with transcatheter thrombolysis, showed a marginal benefit of thrombolysis.[115] However, the study was not randomised, and thrombolysis was associated with higher rates of bleeding.[115] Therefore, until more data are available, and because the long-term outcome of patients with chronic PVT is generally good (5-year survival rate >70%),[116] thrombolysis should be reserved for patients with severe disease after medical treatment has failed.[112]

In children with recent PVT, should management be the same as in adults?

Recommendation

- The same management strategies used in adults may be applied in children except in the neonatal setting and in premature babies **(LoE 4, weak recommendation, consensus).**

PVT most commonly develops during the neonatal period. The most common site is the left portal vein, with most left PVTs being non-occlusive and many resolving spontaneously within days to weeks. It is suggested that >30% of patients will develop portal hypertension. There are no clear factors associated with the development of portal hypertension and its complications. The advantages of systemic anticoagulation need to be weighed against the risks of intracranial bleeding in the premature population. The preferred approach for premature babies is expectant management, to avoid the risk of intracranial bleeding.

A recent systematic review of children aged 12 months to 18 years analysed the management of PVT. In studies where patients received anticoagulation, the estimated rate of portal vein recanalisation was 33%, whereas in studies of patients managed radiologically, complete vessel recanalisation was reported in 41% of cases.[22]

Chronic portal vein thrombosis/portal cavernoma without cirrhosis

In which patients with chronic PVT/portal cavernoma without cirrhosis is anticoagulation recommended to prevent thrombotic events?

Recommendations

- In patients with chronic PVT/portal cavernoma without cirrhosis and with a major and permanent prothrombotic risk factor (Table 3), long-term anticoagulation is recommended to prevent thrombosis recurrence (Fig. 2) **(LoE 1, strong recommendation, strong consensus).**

- In the remaining patients, thrombosis recurrence is less common, but anticoagulation can be considered to prevent thrombosis recurrence. Extension of thrombosis and factor VIII or D-dimer levels may help guide the decision **(LoE 2, weak recommendation, consensus).**

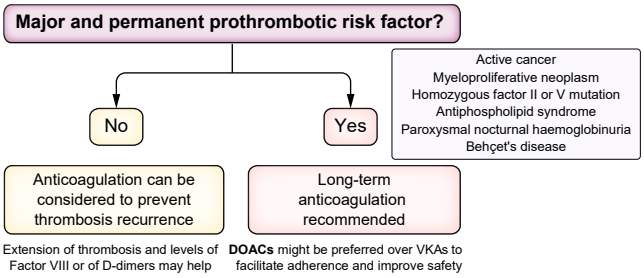

Fig. 2. Indications of anticoagulation in patients with chronic portal vein thrombosis without cirrhosis. DOACs may be preferred over VKAs, except in double/triple positive antiphospholipid syndrome. DOACs, direct-acting oral anticoagulants; VKAs, vitamin K antagonists.

Development of PVT without cirrhosis is associated with one or more general thrombotic risk factors in about two-thirds of cases.[14,92] In terms of safety, a meta-analysis of 7,969 patients from 97 mostly retrospective and observational studies, Valeriani *et al.* found that anticoagulation in patients with recent or chronic PVT without cirrhosis was associated with lower rates of major bleeding events (relative risk [RR] 0.73; 95% CI 0.58-0.92) and of mortality (RR 0.45; 95% CI 0.33-0.60).[117]

In terms of efficacy, in patients with major thrombotic risk factors (*i.e.* personal or 1st degree familial history of spontaneous and recurrent deep vein thrombosis, myeloproliferative neoplasm, active neoplasia, antiphospholipid syndrome, antithrombin deficiency, protein C or S deficiency, homozygous mutation of factor II or factor V Leiden, paroxysmal nocturnal haemoglobinuria, or Behçet's disease), or history of intestinal infarction, long-term anticoagulation should be maintained.[118–120] In this population, anticoagulation therapy has been shown to reduce the rate of thrombus progression and of recurrent thrombosis.[118,119] For instance, in a study by Ollivier *et al.* gathering 50 patients with PVT and a major thrombotic risk factor, a new thrombotic event occurred in 15% of patients at 5 years on anticoagulants *vs.* 58% of the patients not receiving anticoagulants.[121]

In patients without underlying thrombophilia, a retrospective cohort study by Baiges *et al.* observed thrombosis recurrence in 26% of patients who did not receive long-term anticoagulation after a median follow-up of 88 months; factor VIII ≥150% was the only independent factor predicting thrombosis recurrence.[122] In 111 patients with chronic PVT without cirrhosis and no major risk factor for thrombosis, Plessier *et al.* showed, in a prospective randomised controlled trial (RCT), that the incidence of thrombosis was 0 per 100 person-years in patients treated with rivaroxaban 15 mg/day *vs.* 19.7 per 100 person-years in those receiving no anticoagulation (p <0.001; 95% CI 7.49-31.92).[123] In this study, recurrent thrombotic events were splanchnic vein thrombosis in four patients, pulmonary embolism in three patients, and deep vein thrombosis in three patients. After a median follow-up of 30 months, three patients experienced a severe bleeding event: two in the rivaroxaban group, and one in the no anticoagulation group. In a *post hoc* analysis, the authors found that D-dimer ≥500 ng/ml at 1 month after anticoagulation discontinuation was the only feature significantly associated with recurrence of thromboembolism in the non-treated group. Validation of this finding in another prospective study is required.

In patients with chronic PVT/portal cavernoma without cirrhosis, is endovascular portal vein recanalisation with or without TIPS recommended to prevent or to treat complications?

Recommendations

- Patients with chronic PVT/portal cavernoma without cirrhosis, and refractory complications of portal hypertension (recurrent or refractory gastrointestinal bleeding related to portal hypertension, refractory ascites) or portal cavernoma cholangiopathy, should be referred to expert centres for endovascular portal vein recanalisation with or without TIPS (Fig. S1); assessment of feasibility should consider intrahepatic portal branches patency and the extent of portal cavernoma **(LoE 3, strong recommendation, strong consensus).**

- In patients with chronic PVT/portal cavernoma without cirrhosis, without refractory complications of portal hypertension or portal cavernoma cholangiopathy, preventive portal vein recanalisation with or without TIPS is not generally recommended (Fig. S1) **(LoE 4, strong recommendation, strong consensus).**

In patients with chronic PVT/portal cavernoma without cirrhosis, actuarial probability of first bleeding from large oesophageal varices despite primary prophylaxis is about 33% at 3 years; failure to control bleeding or early rebleeding occurs in 17% of these patients.[116] In this population, actuarial probability of rebleeding on secondary prophylaxis is about 50% at 5 years.[116,118] Results of the major studies on portal vein recanalisation with or without TIPS in patients with chronic PVT/portal cavernoma without cirrhosis are presented in Table 6.[124–130]

HE after portal vein recanalisation is uncommon (<10% of cases), and only occurs when TIPS is performed alongside portal vein recanalisation (Table 6).

TIPS may be combined with portal vein recanalisation in two settings: when there is intrahepatic extension of PVT, and/or when intrahepatic vascular resistance remains after portal vein recanalisation, such as in the setting of PSVD.[127,131] While recent studies from interventional radiology expert centres report technical success rates exceeding 75%, procedure-related morbidity occurs in approximately 20% of patients (Table 6). Therefore, patients who have an indication for endovascular portal vein recanalisation should be discussed and managed in expert centres with multidisciplinary approaches.

In regard to the use of anticoagulant therapy during and/or immediately after the procedure, the heterogeneity of the studies makes it difficult to draw firm conclusions.[124,126,127,129] However, it seems reasonable to continue anticoagulation after portal vein recanalisation with/without TIPS, although more data are needed.

Concerning the specific setting of abdominal surgery in patients with PVT/portal cavernoma without cirrhosis, data on portal vein recanalisation to reduce portal pressures prior to surgery are scarce.[132] Marot *et al.* reported results in four patients, who were able to undergo surgery after portal vein

recanalisation, but the sample size is too small to support recommending this approach at present.[127]

In patients with chronic PVT/portal cavernoma without cirrhosis, how should portal cavernoma cholangiopathy be managed to improve outcomes?

Recommendations

- In patients with chronic PVT/portal cavernoma without cirrhosis with symptomatic portal cavernoma cholangiopathy (cholangitis, pancreatitis, jaundice, or pruritus), ursodeoxycholic acid and/or endoscopic or radiological biliary stenting, and/or portal vein recanalisation are recommended to prevent or treat biliary complications (Fig. S2) **(LoE 4, strong recommendation, consensus).**

- In patients with chronic PVT/portal cavernoma without cirrhosis and with asymptomatic portal cavernoma cholangiopathy, endoscopic or radiological biliary stenting, and portal vein recanalisation are not generally recommended (Fig. S2) **(LoE 4, weak recommendation, strong consensus).**

Portal cavernoma cholangiopathy is defined as abnormalities of the intrahepatic and extrahepatic biliary system in a patient with chronic PVT/portal cavernoma without cirrhosis. These abnormalities are partly due to a mass effect related to the pressure of the cavernoma on the bile duct, and to choledochal varices,[133] but also to ischaemia secondary to the extension of thrombosis to small venules of the bile ducts; the former is probably more easily reversible than the latter.[134] Portal cholangiopathy is seen in over 80% of patients with portal vein obstruction;[135,136] magnetic resonance cholangiography combined with magnetic resonance angiography is the reference diagnostic technique.[133] Despite this high prevalence, clinical manifestations (cholecystitis, cholangitis, jaundice, pruritus) appear only in about 20% of patients with chronic PVT/portal cavernoma.

Ursodeoxycholic acid could be beneficial in these patients to control cholestatic symptoms.[133,136]

Endoscopic management, including sphincterotomy, bile stone extraction, mechanical lithotripsy, and biliary stricture dilatation with/without stenting, is the treatment of choice in symptomatic patients.[135] The sphincterotomy needs to be performed with caution due to the bleeding risk from venous collaterals/choledochal varices near the ampullary region.

In case of persistence or recurrence of clinical manifestations despite endoscopic treatment, portal vein recanalisation can be considered: it allows decongestion of the cavernoma, and subsequent reduction of biliary compression.[137] Although data on portal vein recanalisation are scarce in this setting, results seem to be good (Table 6). Surgical treatment with bilio-enteric anastomosis without portosystemic shunt is not recommended due to high morbidity and mortality related to haemorrhage.[138]

In children with chronic PVT/portal cavernoma, should management be the same as in adults?

Recommendations

- Restoration of portal blood flow through Meso-Rex bypass or portal vein recanalisation is recommended in children regardless of the presence of symptoms **(LoE 4, strong recommendation, consensus).**

- When Meso-Rex bypass or portal vein recanalisation are not feasible, watchful management of the complications of portal hypertension is recommended **(LoE 4, strong recommendation, strong consensus).**

- In patients with complications of portal hypertension, porto-caval surgical shunt (spleno-renal or mesenteric to caval shunting) may be considered to delay or avoid LT **(LoE 4, weak recommendation, strong consensus).**

Restoration of portal flow is the main objective to ensure normal growth and development of children with PVT. To achieve this goal, the MesoRex bypass is an established method in experienced centres.[139,140] In children with extrahepatic portal hypertension, complications of portal hypertension should be assessed as they are in patients with cirrhosis,[141,142] because they impact long-term outcomes and may inform management decisions. In patients in whom MesoRex bypass is not feasible, surgical distal spleno-renal shunts or mesocaval shunts may delay the need for LT.[143] Recently, portal vein recanalisation is increasingly being considered by experienced interventional radiologists but little evidence is available.[22,144,145]

Portal vein thrombosis with cirrhosis

In patients with cirrhosis, does the aetiology of cirrhosis and its treatment influence the development of PVT?

Statement

- MASLD may be associated with an increased risk of PVT development. Eradication of HCV does not influence the development of PVT. Data on other causes of cirrhosis are lacking **(LoE 3, consensus).**

Recommendation

- Screening for PVT should be continued regardless of treatment for the aetiology of cirrhosis **(LoE 4, strong recommendation, strong consensus).**

Studies have shown an increased association between PVT and autoimmune liver diseases,[146] as well as metabolic dysfunction-associated steatotic liver disease (MASLD)-related cirrhosis.[147] Other risk factors include the metabolic syndrome, *i.e.* obesity,[148] body mass index,[149] and diabetes.[150] A recent systematic review and meta-analysis found that diabetes,

MASLD/cryptogenic cirrhosis, and hypercholesterolemia were associated with a 1.8-, 1.61- and 3.59-fold increased risk of PVT, respectively.[151] However, apart from hypercholesterolemia, there was significant heterogeneity between studies, which limits the conclusions. The study by Nery *et al.* found alcohol-related cirrhosis and hepatitis C to be associated with PVT, on univariate analysis only.[149] A recent prospective study did not find any aetiological factors independently predictive of the development of PVT in a cohort of 369 patients with cirrhosis followed-up over 5 years.[96] Yet, MASLD represented only 3.5% of the causes of cirrhosis in this study.[96]

Thus, the strongest evidence for the aetiology of cirrhosis influencing the development of PVT is for MASLD. However, whether or not MASLD (lifestyle) interventions modulate the prothrombotic state requires further investigation.

The impact of HCV therapies on PVT development in HCV-related cirrhosis has been investigated. There have been reports of increased risk of PVT following sustained virological response (SVR) with direct-acting antivirals.[152] A large prospective study with over 3 years follow-up compared the risk of non-tumoral PVT in patients who achieved SVR with direct-acting antivirals (n = 354) *vs.* a historic control group with active HCV followed-up until antiviral therapy was commenced (n = 174).[153] The risk of PVT persisted after SVR (2.8%) and was similar to that in the active HCV group (4.5%). Child-Pugh score was the only independent risk factor for PVT. The persistent risk of PVT after SVR in patients with HCV-related cirrhosis has been confirmed in another large study.[154]

Altogether, given that the diagnosis of PVT has significant implications for management strategies that can improve patient outcomes, such as anticoagulation, a strong case can be made to continue screening for PVT irrespective of treatment of the aetiology of cirrhosis.

In patients with cirrhosis, is surveillance for PVT recommended to improve outcomes?

Recommendations

- In patients with cirrhosis who are potential LT candidates, surveillance for PVT (*e.g.* every 6 months) is recommended to improve feasibility and outcomes of LT **(LoE 2, strong recommendation, consensus).**
- In patients with cirrhosis who are not potential LT candidates, surveillance for PVT (*e.g.* every 6 months) is suggested, particularly in those without contraindications to anticoagulation, since anticoagulation has been shown to improve outcomes **(LoE 3, weak recommendation, strong consensus).**

In patients with cirrhosis and an annual risk of HCC of 1.5% or higher, current EASL guidelines advise surveillance for HCC.[81] This is usually done with ultrasound and alpha-fetoprotein every 6 months and may be sufficient for surveillance of PVT. As PVT is often asymptomatic, it may be appropriate to offer surveillance to all patients with cirrhosis.[96]

Studies suggest that PVT is a marker of liver disease progression rather than a cause.

Regarding the risk of first or further decompensation, non-occlusive PVT did not impact the risk of decompensation in a large prospective study including 1,243 patients with Child-Pugh A or B cirrhosis.[149] A prospective study including 241 patients with cirrhosis, mainly compensated, found previous decompensation and thrombocytopenia to be predictors of PVT, but, unlike MELD, PVT predicted neither new decompensation incidence nor transplant-free survival.[155] In a prospective study, including 369 patients with cirrhosis – predominantly Child-Pugh A, but with nearly 50% having a history of previous decompensation – the development of PVT was independently associated with portal blood flow velocity <15 cm/s, low platelet count and a history of variceal bleeding.[96]

Other studies investigated the impact of PVT on the outcome of patients with acute decompensation of cirrhosis. PVT at the time of acute variceal bleeding was found to result in a higher incidence of 5-day treatment failure and 6-week mortality.[156–158] However, a recent observational study of non-occlusive PVT did not support this finding.[159] A large retrospective study found that patients with cirrhosis presenting with acute decompensation had a significantly higher prevalence of PVT (mostly recent, in the main portal vein trunk and non-occlusive) than those without acute decompensation (9.36% *vs.* 5.24%, $p = 0.04$).[160] PVT was also associated with a higher risk of variceal bleeding (47.3% *vs*. 19.73%, $p < 0.01$), but did not influence mortality. Further prospective studies are needed to investigate the role of severity of liver disease and thrombosis characteristics on clinical outcomes and mortality.

The most consistent evidence for an impact of PVT on clinical outcomes is following LT.[161] PVT, particularly occlusive PVT, has a detrimental effect on outcomes after LT, as discussed in the section 'In which patients with PVT and cirrhosis is anticoagulation recommended to improve outcomes'. It is also important to be vigilant for imaging features suggestive of tumoral invasion of the portal vein in patients with HCC on the waiting list. Although "bland" PVT often occurs in HCC, tumour invasion of the portal vein is suggested by ≥3 A-VENA criteria (AFP concentration >1,000 ng/dl; venous expansion; thrombus enhancement; intrathrombus neovascularity; PVT adjacent to HCC) with 80% and 100% positive and negative predictive values, respectively.[162]

Altogether, although the impact of surveillance for PVT on clinical outcomes is debatable, there is a clear need to offer surveillance in all LT candidates. Patients who are not potential transplant candidates, and especially if there is no contraindication to anticoagulation, can also be considered for surveillance as anticoagulation can improve outcomes.[163,164] Ultrasound parameters (especially flow velocity) that predict the risk of PVT and progression should also be considered.

In patients with cirrhosis, is prophylactic anticoagulation recommended to reduce morbidity and mortality?

Statement

- In patients with Child-Pugh B and C cirrhosis without PVT, anticoagulation may reduce morbidity and mortality **(LoE 2, majority agreement).**

The use of prophylactic anticoagulation has been studied in a single-centre RCT in 70 outpatients with cirrhosis (Child-Pugh score 7-10) and no evidence of HCC.[165] Enoxaparin 4,000 IU/day for 48 weeks was compared with no treatment, with rigorous radiological surveillance by ultrasound every 3 months and a CT scan every 6 months. Regarding the primary outcome, 8.8% of patients in the enoxaparin group developed PVT compared to 27.7% in the control group. Furthermore, patients in the enoxaparin group had less decompensation and better survival than patients in the control group. There was also a lower incidence of bacterial infections in the enoxaparin arm. There was no difference in safety outcomes, although patients treated with enoxaparin had a higher rate of thrombocytopenia, which returned to baseline after the drug was stopped. Although these results demonstrate a benefit of LMWH in selected patients with cirrhosis and delayed development of PVT, limitations of the study include the small sample size and lack of a placebo arm, which may have introduced selection bias. The lack of an anti-Xa assay was also worth noting.

To address some of the limitations of the above study, a phase III randomised placebo-controlled trial of rivaroxaban 10 mg/24 h in 90 patients with cirrhosis (Child-Pugh score 7-10) over a median follow-up of 10 (0.4–24) months was conducted.[164] The composite primary outcome, which differed from the study above,[165] was the development of portal hypertension-related complications or death/transplantation. The trial was stopped before reaching the target sample size of 160 due to low recruitment and termination of funding. Overall, there was no difference in the primary outcome (HR 0.52, 95% CI 0.25-1.07, $p = 0.069$) on intention-to-treat analysis. However, statistical significance was achieved when adjusting for baseline Child-Pugh score, previous decompensation and non-selective beta-blocker (NSBB) use (HR 0.45 95% CI 0.2-0.9, $p = 0.038$), with the benefit seen especially in Child-Pugh B patients. There was no difference in individual decompensating events or PVT. Non-portal hypertension-related bleeding was more frequent in the rivaroxaban arm (33.8% *vs*. 13.6%, $p = 0.04$). Hepatotoxicity was also more frequent with rivaroxaban (13.6% *vs.* 3.1%, $p = 0.046$). Although underpowered, this study shows the potential for a beneficial effect of a DOACs in patients with cirrhosis and moderate liver impairment. Further studies are needed to clarify safety issues and definitively establish efficacy.

In patients with PVT and cirrhosis, should work-up for risk factors for thrombosis be performed to guide management?

Recommendation

- Work-up for risk factors for thrombosis is not recommended to guide management **(LoE 2, strong recommendation, consensus).**

The risk factors for the development of PVT have been well described. Clinical risk factors associated with PVT development include decreased portal venous blood flow, low platelet count, history of variceal bleeding, presence of oesophageal varices, and prolonged prothrombin time.[96,149] This would suggest that the severity of underlying liver disease is an important factor. Risk factors for thrombosis identified in PVT without cirrhosis (*e.g.* myeloproliferative neoplasm, inherited thrombophilia) are not relevant for PVT in patients with cirrhosis. Indeed, Nery *et al.* found that the prevalence of G20210A factor II and factor V Leiden gene mutations in their study population was comparable to a French cohort without a history of thromboembolism.[149] Moreover, there was no association between these two mutations and the risk of PVT development. Further evidence for the lack of relevance of risk factors for thrombosis in cirrhotic PVT is presented by Turon *et al.*.[96] This large prospective study found no relationship between inherited or acquired thrombosis risk factors and the development of PVT. Indeed, as in the study by Nery *et al.*, G20210A factor II mutation and factor V Leiden were not associated with PVT development. Conversely, levels of procoagulant factor X were independently associated with PVT development. In this study, a comprehensive analysis of inflammatory factors, including neutrophil extracellular traps, did not reveal any variables independently associated with the development of PVT.

Altogether, based on these studies, there is no indication to analyse specific risk factors for thrombosis in cirrhosis, unless personal or familial medical history or laboratory testing suggests a specific thrombophilic condition (*e.g.* elevated blood cell count for myeloproliferative neoplasms). Clinical and imaging variables commensurate with the severity of underlying cirrhosis appear to have greater predictive ability.

In which patients with PVT and cirrhosis is anticoagulation recommended to improve outcomes?

Recommendations

- In patients with cirrhosis and PVT who are potential LT candidates, anticoagulation should be used regardless of degree of occlusion or extension of PVT, to improve feasibility and outcomes of LT **(LoE 3, strong recommendation, strong consensus).**

- In patients with cirrhosis who are not potential LT candidates, anticoagulation may be used for PVT with total occlusion or >50% occlusion of the main portal vein, with or without superior mesenteric vein extension, to improve outcomes **(LoE 3, weak recommendation, strong consensus).**

- In patients with cirrhosis who are not potential LT candidates, anticoagulation may be considered for PVT with <50% occlusion of the main portal vein, which progresses over 3-6 months or extends to the superior mesenteric veins, to improve outcomes **(LoE 3, weak recommendation, strong consensus).**

- In patients with cirrhosis who are not potential LT candidates, and who have PVT with <50% occlusion of the main portal vein, surveillance is recommended and anticoagulation can be considered to improve outcomes **(LoE 4, weak recommendation, strong consensus).**

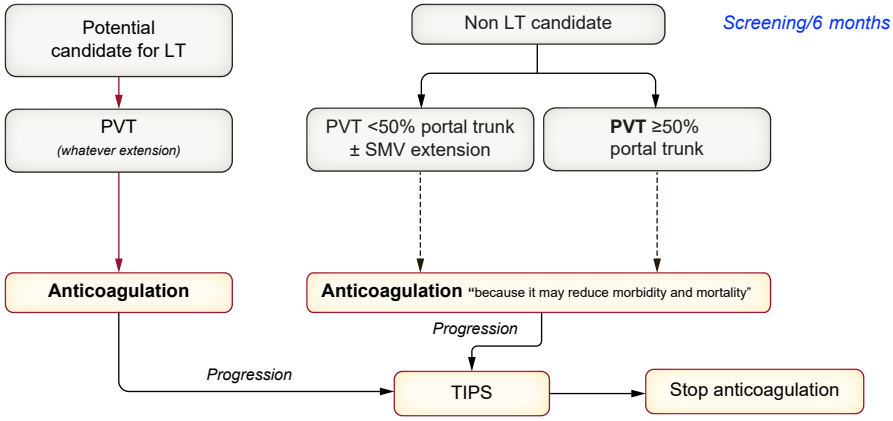

Fig. 3. Indications of anticoagulation in patients with PVT and cirrhosis. Full lines indicate the recommended indications for anticoagulation. Dashed lines indicate possible indications for anticoagulation. LT, liver transplantation; PVT, portal vein thrombosis; SMV, superior mesenteric vein; TIPS, transjugular intrahepatic portosystemic shunt.

It has been shown that the natural history of PVT has minimal impact on hard clinical outcomes in compensated cirrhosis,[149] although the presence of PVT at the time of variceal bleeding and LT can influence outcomes.[161]

Anticoagulation in cirrhotic PVT was studied in a meta-analysis of predominantly retrospective studies gathering 353 patients. Anticoagulation resulted in higher rates of recanalisation (71% *vs.* 42%) and complete recanalisation (53% *vs.* 33%), and a lower rate of PVT progression (9% *vs.* 33%), without an increase in bleeding episodes.[166] A recent individual patient data meta-analysis confirmed these findings in 500 patients with mostly non-occlusive PVT from five cohort studies.[166] Recanalisation was significantly higher with anticoagulation (58% *vs.* 33%; adjusted odds ratio 3.5; 95% CI 2.2-5.4) independent of severity of PVT. Anticoagulation resulted in reduced all-cause mortality (adjusted sub-distribution HR 0.6; 95% CI 0.5-0.7) over a median follow-up of 26 months, independent of PVT severity and recanalisation. The median duration of therapy was 9 (7-13) months, and longer therapy reduced mortality. However, there was an increased risk of non-portal hypertension-related bleeding (9.7% *vs.* 1.7%, p <0.001), which was mainly gastrointestinal. It is worth noting that none of the studies in these two meta-analyses used DOACs.

PVT is known to have an impact on LT outcomes. A meta-analysis showed that the presence of PVT at the time of LT increased 1-year mortality (odds ratio 1.38; 95% CI 1.14-1.66), although there was significant heterogeneity.[161] Complete PVT also resulted in significantly higher 30-day post-transplant mortality compared with partial PVT (odds ratio 5.65; 95% CI 2-15.96), without significant heterogeneity.

Anticoagulation is most effective if started within 6 months of diagnosis of PVT.[167] LMWH has been shown to be more effective than warfarin with regard to complete PVT resolution.[166] Of note, the anti-Xa assay can lead to excessive dosing due to reduced levels of antithrombin, especially in more advanced cirrhosis.[168] Dose reductions of ≥30% can be considered.[169] Fondaparinux offers the advantage of once-daily fixed dosing and a reduced risk of heparin-induced thrombocytopenia, with potentially greater efficacy than LMWH but with increased risk of bleeding. Further studies are needed.[170] VKAs are the mainstay of long-term therapy and offer the advantage of once-daily oral therapy. INR monitoring can be challenging due to elevated baseline INR. DOACs are discussed in the next section.

A platelet count <50x10^9/L with anticoagulation is associated with increased bleeding risk.[171] An individualised approach is recommended, in consultation with a haematologist, if the platelet count is <50x10^9/L.[40] After cessation of anticoagulation, 30-40% of patients develop recurrent thrombosis between 2-5 months.[171–173] Therapy for primary or secondary prevention of variceal bleeding is commenced if indicated.[174]

Thus, a robust case can be made for anticoagulation in candidates on the waiting list for LT regardless of the degree of PVT (Fig. 3). However, anticoagulation should also be considered in other patients with PVT and >50% occlusion of main portal vein regardless of extension of PVT.[40] In patients with PVT and <50% occlusion, surveillance is advised, and anticoagulation considered where PVT progresses over 3-6 months or if there is SMV extension. In other patients who are not transplant candidates with PVT <50%, surveillance should be continued and anticoagulation considered (Fig. 3).

In patients with PVT and cirrhosis, are direct oral anticoagulants recommended over vitamin K antagonists or low-molecular-weight heparin to reduce morbidity and mortality?

Recommendation

- Direct oral anticoagulants can be used in patients with PVT and Child-Pugh A or B cirrhosis; however, owing to insufficient evidence, they cannot be recommended over vitamin K antagonists or low-molecular-weight heparin to reduce morbidity and mortality. In patients with Child-Pugh C cirrhosis, direct oral anticoagulants are not recommended **(LoE 3, weak recommendation, consensus).**

There has been much interest in the off-label use of DOACs in PVT due to ease of oral administration without the requirement for monitoring. Observational studies have shown at least

similar or better efficacy to VKAs/LMWH[175–178] without increased risk of bleeding in early cirrhosis,[179] but higher spontaneous bleeding risk in patients with Child-Pugh class B/C than in Child-Pugh A cirrhosis (at 12 months, 37% *vs.* 16%, respectively; subdistribution HR 3.2; 95% CI 2-16.9; p <0.001).[180]

The pharmacokinetics and pharmacodynamics of DOACs in patients with cirrhosis differ from those in individuals without cirrhosis. Based on pharmacokinetic and pharmacodynamic data, apixaban and edoxaban have a particularly compelling pharmacological profile in patients with cirrhosis. A detailed analysis of DOACs in cirrhosis has recently been provided elsewhere.[181] Reversal agents (idarucizumab for dabigatran, and andexanet alfa for apixaban, edoxaban, and rivaroxaban) are now more widely available.

Therefore, there is a role for DOACs in Child-Pugh class A and B cirrhosis. Further prospective study is needed to optimise patient selection and choice of DOACs. Controlled prospective studies comparing DOACs with VKAs or LMWH are advised.

In patients with PVT and cirrhosis, when should TIPS be considered over anticoagulation alone to reduce morbidity and mortality?

Recommendations

- In patients with cirrhosis and PVT who have complications of portal hypertension, such as variceal bleeding or recurrent ascites, TIPS may be considered over anticoagulation alone to reduce morbidity **(LoE 2, weak recommendation, strong consensus).**

- In patients with cirrhosis and PVT which progresses despite anticoagulation, TIPS may be considered over anticoagulation alone to reduce morbidity **(LoE 2, weak recommendation, consensus).**

TIPS is possible in PVT and cirrhosis, even in technically challenging conditions, such as cavernoma[182] or fully occlusive PVT, using transjugular, transplenic or transmesenteric routes,[183–185] or in combination with mechanical thrombolysis.[186]

The safety and efficacy of TIPS for PVT in cirrhosis has been studied in a meta-analysis of 367 patients.[187] PVT was chronic in 87% and complete in 46% (SMV involvement in 55%). A recanalisation rate of 81% was reported, which was lower in patients with cavernous transformation and SMV involvement. Significant heterogeneity prevented analysis of recent *vs.* chronic PVT. The 12-month patency rate with covered stents (n = 201 patients) was 89%. HE was present in 23%. There were important safety considerations, with a 10% major complication rate in expert centres. Where thrombectomy and thrombolysis were performed with TIPS, the major complication rate increased to 18% with six deaths. Limitations of the meta-analysis are that it included predominantly observational studies and that its findings may not be generalisable to less expert centres.

Another meta-analysis compared TIPS (n = 148) with anticoagulation (n = 179), using data from seven predominantly observational studies.[188] The authors observed that these interventions (TIPS or anticoagulation) resulted in high rates of recanalisation compared to no anticoagulation or TIPS (odds ratio 4.56; 95% CI 2.46–8.47). Anticoagulation was associated with reduced mortality (odds ratio 0.28; 95% CI 0.08–0.95), while TIPS was not (odds ratio 1.10; 95% CI 0.23–5.16), suggesting that the beneficial effect of anticoagulation on mortality is independent from its impact on portal vein recanalisation.

There is a paucity of data directly comparing TIPS alone and anticoagulation in PVT with cirrhosis. Two RCTs that compared TIPS with endoscopic plus drug therapy for the secondary prevention of variceal haemorrhage included anticoagulation in both arms.[189,190] TIPS was more effective in preventing variceal rebleeding without an increase in adverse events. PVT recanalisation was significantly higher with TIPS, at up to 95%, compared to only 19.4% without TIPS. However, there was no difference in survival. A recent retrospective study compared TIPS *vs*. endoscopic therapy plus anticoagulation following variceal bleeding in 66 patients.[191] TIPS was associated with a significantly higher rate of recanalisation (85.5% *vs*. 19.6%), a lower rate of rebleeding (31% *vs.* 51%), but a higher rate of HE (25.8% *vs.* 5.7%). There was no difference in survival. Limitations of the study include the lack of NSBB use in the control arm and the small sample size. It is worth noting that in all these studies anticoagulation was commenced after variceal eradication in the non-TIPS arm. This delay in anticoagulation, whilst consistent with current guidelines, may partly explain the higher recanalisation rate in the TIPS arm where anticoagulation was initiated after successful TIPS.

TIPS should be considered for patients with PVT and portal hypertension-related complications, especially variceal bleeding, and in transplant candidates to improve post-transplant outcomes.[192] In the absence of such indications, anticoagulation is the first-line therapy, with TIPS reserved for cases unresponsive or progressive after 6 months.

In patients with PVT and cirrhosis who undergo TIPS, should anticoagulation be administered to improve recanalisation rates?

Recommendation

- Routine anticoagulation is not recommended to improve recanalisation rates after TIPS **(LoE 2, strong recommendation, consensus).**

Successful TIPS implantation in PVT with cirrhosis restores portal venous flow and addresses one of the pathophysiological mechanisms in Virchow's triad.[193] There are studies investigating the role of anticoagulation following TIPS for PVT in cirrhosis. The only RCT of covered TIPS did not show a clear benefit of anticoagulation following TIPS with similar rates of portal vein recanalisation (83.6% *vs*. 71.8%).[194] Similarly, a systematic review and meta-analysis found that in patients with PVT at the time of TIPS, additional anticoagulation did not

impact on recanalisation nor TIPS patency rates.[187] It should be noted that this review was limited by inclusion of legacy studies using uncovered stents and inconsistent anticoagulation/antiplatelet regimens.

In patients with PVT and cirrhosis at the time of LT, should anticoagulation be used after LT to prevent recurrence of PVT?

Recommendations

- In patients with cirrhosis and Yerdel grade 1 or 2 PVT (Table S1) at the time of LT, anticoagulation after transplantation is not suggested to prevent recurrence of PVT **(LoE 4, weak recommendation, consensus).**

- In patients with cirrhosis and Yerdel grade 3 or 4 PVT (Table S1) at the time of LT, no recommendation can be made in favour or against anticoagulation after transplantation to prevent recurrence of PVT **(LoE 4, weak recommendation, consensus).**

PVT is found in 7-8% of patients at the time of LT and occlusive PVT in particular leads to adverse post-transplant outcomes.[161,195] Anticoagulation is recommended in patients with cirrhosis and PVT on the LT waiting list.[40] There is less evidence for the role of therapeutic anticoagulation in patients with cirrhosis and PVT following LT. There is only one retrospective two-centre study comparing the impact of therapeutic anticoagulation with heparin followed by VKAs for 3 months (n = 113) *vs.* no anticoagulation (n = 122) in patients with Yerdel 1 and 2 PVT, following LT.[196] Patients all had physiological end-to-end portal vein anastomosis. In patients with known PVT prior to surgery (70%), 65% had therapeutic anticoagulation on the waiting list, with 38% having complete recanalisation. At 1 year after transplantation, there was no difference in PVT recurrence with or without anticoagulation (5.1% *vs*. 2.1%, p = 0.39). However, in the anticoagulation group, hospital stay was significantly longer, while bleeding events and the need for surgical revision were more common. There was no difference in patient or graft survival. The findings remained robust following subgroup analysis of just Yerdel 2 PVT and PVT at the time of transplantation.

Another retrospective study, without a control group, and including predominantly patients with Yerdel Grade 1-2 PVT showed no recurrent thrombosis after 6 months of anticoagulation (heparin followed by VKAs) post LT.[197] Rizzari *et al.* studied the impact of combined heparin and aspirin following LT in patients with PVT (Yerdel 1 (58%), Yerdel 2-3 (42%).[198] The PVT recurrence rate was high at up to 22.6%. Low intra-operative portal vein flow was associated with higher PVT recurrence, which could indicate that factors other than anticoagulation are important. To date there are no studies using DOACs following LT in patients with PVT and cirrhosis.

Porto-sinusoidal vascular disorder

Porto-sinusoidal vascular disorder (PSVD) entails a group of liver vascular entities that commonly damage the intrahepatic vessels at the level of the portal venules and/or the sinusoids and share a similar clinical phenotype and evolution, primarily characterised by the development of portal hypertension in the absence of cirrhosis. The term PSVD was coined in 2017 at a monothematic conference organised by VALDIG, and subsequently endorsed by the Baveno VII Expert Conference in 2022, in order to unify the terminology worldwide for a group of entities that had been given different names depending on the region of the world they were diagnosed. Commonly used names were “non-cirrhotic portal fibrosis” in India, “idiopathic portal hypertension” in Japan or “hepatoportal sclerosis”, “incomplete septal cirrhosis” or “nodular regenerative hyperplasia” or “obliterative portal venopathy” in Western countries. The rationale behind homogenising terminology was to highlight commonalities and facilitate the understanding of rare conditions with a believed common underlying biological mechanism and therefore common therapeutically actionable targets.

The presence of other causes of chronic liver disease is no longer an exclusion criterion, as PSVD can coexist with conditions like excessive alcohol consumption, HBV or HCV infection, autoimmune hepatitis, and metabolic syndrome.[199] Additionally, it can coexist with PVT without portal cavernoma and a history of solid organ transplantation, including LT. However, conditions affecting the hepatic veins (such as BCS) and liver diseases causing microvascular damage (such as sarcoidosis, congenital hepatic fibrosis, SOS, bone marrow transplantation, schistosomiasis, cardiac failure, and liver infiltration by tumour cells) are not considered within the definition of PSVD.[102]

In patients with liver-related abnormalities, which features should raise a suspicion of PSVD over other liver diseases?

Recommendations

- In patients with signs of portal hypertension, LSM <10 kPa, HVPG <10 mmHg, and smooth liver surface together with a normal-size or enlarged segment IV, especially in the presence of associated disorders or drugs listed in Table 5, should raise suspicion of PSVD **(LoE 3, strong recommendation, strong consensus).**

- In patients without signs of portal hypertension, unexplained liver blood test abnormalities should raise suspicion of PSVD, particularly in the presence of associated disorders or exposure to drugs listed in Table 5 **(LoE 3, strong recommendation, strong consensus).**

While histological signs may be evident in asymptomatic patients, even in the absence of clinical indicators of portal hypertension, PSVD is most commonly diagnosed when portal hypertension is present. Variceal bleeding is the most frequently reported form of presentation, affecting >50% of symptomatic patients.[97,107,200] It is essential to consider PSVD in the differential diagnosis for all patients with unexplained abnormalities in liver blood tests, regardless of the presence or absence of portal hypertension.

Table 5. Conditions associated with PSVD.

Associated condition	Diagnostic test	When to search	Impact on therapeutic choice	Notes
Exposure to drugs (*i.e.* didanosine, zidovudine, stavudine, lamivudine, azathioprine, oxaliplatin)	Clinical evaluation	Routinely	Consider stopping the drug	
HIV infection	Blood test	Routinely		Evaluate exposure to inosine analogues
Genetic mutations (*DGUOK, FOPV, FCHSD1, GIMAP5, HLA-DR 3, HRG, KCNN3, TRMT5,* telomere-related genes, other syndromic diseases[218]	Genetic testing	Familiar aggregation; childhood diagnosis of PSVD	Counselling	
Prothrombotic disorders (antithrombin deficiency, antiphospholipid syndrome, protein C deficiency, protein S deficiency, prothrombin gene mutation, factor V Leiden mutation, paroxysmal haemoglobinuria, factor VIII elevation)	Thrombophilia study	If thrombotic events	May determine duration of anticoagulation	
Haematological disorders (myeloproliferative neoplasm, idiopathic thrombocytopenic purpura, aplastic anaemia, Hodgkin's lymphoma, marginal B cell lymphoma, multiple myeloma, monoclonal gammopathy of uncertain significance, Castleman disease, chronic lymphoid leukaemia …)	Laboratory testing, CT scan, bone marrow biopsy, *JAK2* mutation Plasma protein electrophoresis, NGS	Large splenomegaly and normal or slightly elevated platelets	Specific aetiological treatment	
Immunological disorders (common variable immunodeficiency syndrome, Inflammatory bowel disease, celiac disease, hypothyroidism, systemic lupus erythematosus, vasculitis, Sjögren, rheumatoid arthritis, psoriasis, Grave's disease, myasthenia gravis, autoimmune nephropathy, POEMS syndrome, Behçet's disease, dermatomyositis, sacroiliitis, Still's disease …)	Laboratory tests, CT scan	If specific clinical suspicion	Aetiological treatment	
Recurrent abdominal infections	Laboratory tests, CT scan	If specific clinical suspicion	Antibiotic treatment	

PSVD, porto-sinusoidal vascular disorder.

Thrombocytopenia (platelet count <150x10^9/L) is the most common biochemical abnormality, seen in up to 60% of patients with PSVD.[107] Diagnostic suspicion can be heightened by assessing specific features in both invasive and non-invasive tests, as well as considering the association with other relevant diseases. The presence of splenomegaly is one of the most frequent signs, and in comparison to cirrhosis, patients with PSVD tend to have larger spleens.[107,200–202]

Up to 50% of patients may exhibit hepatic vein-to-vein communications that prevent adequate obliteration during hepatic vein catheterisation. Furthermore, when HVPG can be accurately measured, a value <10 mmHg in a patient with clinical signs of portal hypertension is suggestive of PSVD. Liver and spleen elastography are also useful, with LSM <10 kPa in the presence of portal hypertension raising suspicion.[100,101] A high spleen-to-liver stiffness ratio is helpful in distinguishing PSVD from cirrhosis.[203,204]

CT scans and MRI can also be useful. The presence of signs of portal hypertension along with a smooth liver surface and a normal-sized or enlarged segment IV should raise suspicion.[98] Marginal atrophy, compensatory central hypertrophy, abnormal intrahepatic branches or right liver atrophy/hypotrophy in combination with caudate lobe hypertrophy are imaging features that aid in differentiating PSVD from cirrhosis.[205,206] Benign focal lesions, often FNH-like nodules detected on contrast-enhanced MRI, are more common in PSVD than in cirrhosis, aiding in the differential diagnosis.[207]

In about 50% of patients, an associated disorder (such as immune/coagulation disorders, congenital or hereditary diseases) or exposure to specific drugs (such as didanosine, azathioprine, oxaliplatin) may be identified and can be helpful in raising suspicion (Table 5).[106]

Table 6. Endovascular portal vein recanalisation, combined or not with TIPS, in patients with chronic portal vein thrombosis/portal cavernoma without cirrhosis.

Study	Qi, Dig Dis Sci 2012[124]	Kallini, Hepatol 2016[125]	Klinger, Z Gastroenterol 2018[126]	Marot, Diag Interv Imaging 2019[127]	Knight, Hepatol 2021[128]	Artru, JHEP Rep 2022[129]	Wei, J Vasc Interv Radiol 2023[130]
Design of the study	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
n	20	5	17	15	39	31	54
Indication for PVR (%):*							
Gastrointestinal bleeding	100	60	76	47	62	42	100
Abdominal pain	0	40	6	13	59	23	NA
Prior to abdominal surgery	0	0	0	27	0	13	NA
Portal cholangiopathy	0	0	6	13	3	10	NA
Other	5	0	12	0	15	12	NA
Associated TIPS (%)	**100**	**100**	**71**	**0**	**100**	**0**	**54**
Access (%):							
Transhepatic	70	0	100	100	36	97	NA
Transsplenic	25	100	0	0	49	NA	NA
Other	5	0	0	0	15	NA	NA
Technical success (%)	35	100	76	87	100	87	78
Complications related to the procedure (%):							
Adverse events	5	NA	12	7	23	20	NA
Death	0	NA	6†	0	0	0	NA
Primary patency	86% after a median follow-up of 20 months	100% at 3 months	70% at 1 year	77% at 2 years	63% at 3 years	73% at 5 years	70% after a mean follow-up of 40 months
Outcomes	86% of patients free of PH complications after a median follow-up of 20 months; no HE; 2 liver-related deaths (TIPS failure in both)	NA	82% of patients free of PH complications after a median follow-up of 23 months; no HE; 1 liver-related death	87% of patients free of PH complications after a mean follow-up of 42 months; no liver-related death	87% of patients improved clinical condition and/or biochemical parameters after ≥6 months of follow-up; transient HE in 5% and refractory HE in 3%; acute heart failure in 3%	78% of patients free of PH complications at 5 years; improvement of sarcopenia; no liver-related death; no HE	Cumulative variceal rebleeding rates: 28% in the TIPS groups *vs.* 4% without TIPS
Long-term anticoagulation after PVR (%)	100 for 6-12 months, and then only in patients with TIPS dysfunction	NA	82	77	90	70	NA

HE, hepatic encephalopathy; PH, portal hypertension; PVR, portal vein recanalisation; TIPS, transjugular intrahepatic portosystemic shunt.
*Sum can exceed 100% due to the possibility of several indications in a patient.
†Death related to nosocomial pneumonia.

Table 7. Diagnostic criteria for PSVD.

	Signs of portal hypertension	Histological lesions of PSVD
Specific	Gastric oesophageal, or ectopic varices Portal hypertensive bleeding Porto-systemic collaterals at imaging	Obliterative portal venopathy Nodular regenerative hyperplasia Incomplete septal fibrosis (also called incomplete septal cirrhosis); this latter feature can only be assessed on liver explants and not on liver biopsies
Non-specific	Ascites Platelet count <150,000/L Spleen size ≥13 cm in the largest axis	Portal tract abnormalities (multiplication, dilation of arteries, periportal vascular channels, and aberrant vessels) Architectural disturbance: irregular distribution of the portal tracts and central veins Non-zonal sinusoidal dilatation Mild perisinusoidal fibrosis

PSVD, porto-sinusoidal vascular disorder.
Diagnosis is based on the absence of cirrhosis plus the presence of histological alterations suggestive of this disease with or without signs of portal hypertension.
Diagnosis of PSVD requires the exclusion of cirrhosis and of other causes of portal hypertension, together with one of the following criteria: (i) at least one feature specific for portal hypertension; (ii) at least one histologic lesion specific for PSVD; or (iii) at least one feature not specific for portal hypertension together with at least one histologic lesion compatible although not specific for PSVD.

In patients suspected of having PSVD, what modality should be used to establish the diagnosis?

Recommendation

- A liver biopsy should be performed to make a diagnosis of PSVD (Table 7) **(LoE 3, strong recommendation, strong consensus).**

The diagnosis of PSVD relies on histological criteria. Liver damage can be very subtle and unevenly distributed within the liver parenchyma, requiring a comprehensive evaluation by a trained pathologist and a "good-quality" biopsy, which should be over 20 mm in length and without excessive fragmentation (or considered adequate for interpretation by an expert pathologist).[40] Recent data suggest that a 15 mm liver biopsy may be sufficient.[208] The histological diagnosis is primarily founded on the exclusion of cirrhosis and identification of characteristic histological lesions.

Obliterative portal venopathy (portal vein stenosis), nodular regenerative hyperplasia, and incomplete septal fibrosis/cirrhosis are regarded as the most specific pathological features of PSVD.[102] The presence of any of these signs, in the absence of cirrhosis, is sufficient for the diagnosis of PSVD, even without signs of portal hypertension.[40,102,209]

Histological lesions compatible, although less specific for PSVD, include herniated portal vein branches, hypervascularised portal tracts, periportal abnormal vessels, sinusoidal dilatation, and architectural disturbance characterised by the irregular distribution of portal tracts and central veins, non-zonal sinusoidal dilatation (SD), and mild perisinusoidal fibrosis (Table 7). If found in patients with signs of portal hypertension (specific or not), and in the absence of cirrhosis, these lesions establish the diagnosis of PSVD.

Moreover, the diagnosis of PSVD can also be established in the absence of elementary histological lesions in patients exhibiting specific signs of portal hypertension (such as gastric, oesophageal, or ectopic varices, portal hypertensive bleeding, and porto-systemic collaterals on imaging), and with no evidence of cirrhosis on biopsy.

In patients with PSVD, what work-up should be carried out to identify conditions associated with PSVD?

Recommendations

- An extensive work-up for HIV infection, thrombophilia, haematological disorders, immune/inflammatory/systemic diseases, as well as exposure to drugs, is recommended to identify conditions associated with PSVD (Table 5) **(LoE 3, strong recommendation, strong consensus).**
- Routine genetic testing for familial forms of PSVD cannot be recommended systematically **(LoE 4, weak recommendation, consensus).**
- Initial work-up should also include laboratory investigations and contrast-enhanced imaging, preferably CT, to search for other causes of liver disease and evaluate patency of the splanchnic venous system **(LoE 3, strong recommendation, strong consensus).**

Statement

- Conditions associated with PSVD have prognostic value. It is not known whether treating associated conditions has an impact on PSVD outcome **(LoE 3, strong consensus).**

PSVD has been linked to HIV infection, which affects 8% of patients with PSVD, although the frequency appears to have decreased over time, likely due to the discontinuation of inosine analogues in HIV treatment schemes.[107] Immune system disorders are the most commonly associated conditions, affecting up to 32% of patients with PSVD.[107] Other reported disorders include inflammatory bowel disease (6%),[210] prothrombotic conditions (such as protein C and S deficiency),[211] blood diseases (like aplastic anaemia and myeloproliferative diseases,[102] among others), and exposure to drugs including azathioprine, oxaliplatin, didanosine, and stavudine.[212,213] In some instances, more than one of these conditions may coexist.

Familial studies have suggested a genetic basis for PSVD, with several mutations identified in select cohorts, such as *DGUOK, FOPV, FCHSD1, GIMAP5, HLA-DR 3, HRG, KCNN3, TRMT5,* telomere-related genes.[214–218] However, large-scale validation is lacking. While the presence of these genetic entities may assist in establishing the diagnosis, there is currently insufficient data to recommend actively searching for them.

PSVD can coexist with other causes of chronic liver disease (*e.g.* HBV or HCV infection) and should be investigated.

In patients with PSVD, is surveillance recommended to detect HCC or PVT over no surveillance?

Recommendations

- Surveillance for PVT every 6 months is recommended **(LoE 4, strong recommendation, consensus).**
- Surveillance for HCC cannot be recommended **(LoE 4, strong recommendation, strong consensus).**

The risk of developing PVT during follow-up is substantial, and active screening is recommended.[40] However, there is a lack of data to determine the most effective screening method and the optimal screening interval for patients with PSVD. A reasonable approach may be to adopt, in patients with PSVD and signs of portal hypertension, the same screening strategy used in cirrhosis for HCC screening, namely ultrasound every 6 months.[40] The natural history of PSVD in patients without signs of portal hypertension is unknown, so no recommendations can be made regarding follow-up strategies.

While PSVD is less likely than other liver diseases to predispose patients to the formation of hyperplastic nodules, when nodules do occur, they typically resemble nodular hyperplasia. The development of HCC in PSVD is exceptionally rare, with only a few isolated cases reported in the literature.[220,221] A recent European study found that liver nodules occurred in approximately 12% of PSVD cases, with only 3 (0.5%) cases of HCC.[107] In another multicentric study evaluating patients with PSVD undergoing LT, only 2 (2.5%) cases had HCC, and one of them also had coexisting HBV infection.[222]

In patients with PSVD, is prophylactic anticoagulation for PVT recommended over no treatment to reduce the incidence of thrombotic events?

Statement

- No recommendation can be made regarding anticoagulation therapy to prevent the development of PVT due to the absence of data **(LoE 4, strong consensus).**

The prevalence of prothrombotic disorders (8.7% in the most recent series[107]) and high incidence of PVT in patients with PSVD raises the question of prophylactic anticoagulation. Indeed, PVT is a common feature of PSVD, both at the time of diagnosis and during follow-up. Consequently, it is advisable to assess the patency of the portal venous system using CT scans or contrast-enhanced MRI at initial work-up. Reported incidence ranges from 16–33% at 5 years, if PVT was not present at the time of PSVD diagnosis[97,107,219] In the largest and most recent PSVD series, 29.5% of patients experienced PVT at some point in their clinical course.[107] PVT predominantly occurs in the extrahepatic portal vein trunk,[107,224] and its detection may be missed. Moreover, autopsy studies have shown obliteration of large portal veins in explanted livers in as many as 67% of cases.[223] Involvement of mesenteric veins has been reported in up to 4-5% of the patients with PVT, potentially leading to life-threatening PVT complications such as mesenteric infarction.[225] Furthermore, thrombosis often affects intrahepatic small- and medium-sized portal vein branches,[226,227] causing obliterative portal venopathy, and is believed to contribute to liver disease development and progression due to impaired intrahepatic circulation.

On the other side, only HIV aetiology, ascites, and the presence of high-risk varices – but not the existence of prothrombotic disorders – have been linked to the risk of PVT in a large recent series.[107] Moreover, there is no clear evidence that PVT worsens the outcome of liver disease in the absence of mesenteric infarction. Finally, anticoagulation can lead to severe adverse events, with bleeding occurring in 9% of patients in the En-vie cohort and being severe in up to 5%.[92]

Given this information, the use of prophylactic anticoagulation to prevent PVT development has been a subject of discussion in recent years. This has led to the initiation of an RCT evaluating the role of apixaban in PVT prevention (ClinicalTrials.gov ID NCT04007289). Until the results of this study are available, the potential benefits of prophylactic anticoagulation remain unproven.

In patients with PSVD and severe or refractory portal hypertension-related complications, is TIPS or LT recommended to reduce morbidity and mortality?

Recommendations

- In patients with PSVD and severe or refractory portal hypertension-related complications, TIPS and/or LT are recommended to improve long-term outcomes **(LoE 3, strong recommendation, strong consensus).**
- Pre-LT evaluation should include careful evaluation of associated conditions that may impact outcome **(LoE 3, strong recommendation, strong consensus).**

TIPS has been shown to be highly effective in treating severe and/or refractory complications related to portal hypertension in patients with PSVD. In a cohort of 41 patients with PSVD treated with TIPS, the 2-year survival rate was 80%. It is important to note that the presence of significant extrahepatic comorbidities and renal failure (characterised by a serum creatinine level >100 μmol/L or 1.13 mg/dl) was associated with an increased risk of mortality following TIPS; these factors should be meticulously evaluated before considering TIPS placement. HE occurred in up to 31% of cases, but it generally

responded well to medical therapy.[228] Importantly, the presence of TIPS does not negatively affect the outcome of patients undergoing LT.[222]

LT remains a viable option for patients with PSVD who suffer from refractory complications of portal hypertension. In the largest study available, which included 79 patients from 28 European centres with a median follow-up of 37 months after LT, the 5-year survival rate after LT was 69%. This rate increased to 85% in patients without severe associated conditions. However, in patients with severe associated conditions, the potential risks and benefits of transplantation must be discussed thoroughly on a case-by-case basis, as outcomes are worse. Additionally, pre-transplant hyperbilirubinemia or creatinine levels >100 μmol/L are associated with poor post-LT outcomes.[222]

Reported recurrence of PSVD after LT varies between 4% and 13%.[222,229,230] It is important to note that these studies lack comprehensive evaluation after transplantation, and the incidence of subclinical PSVD without portal hypertension in transplanted livers remains unknown.

In children suspected of having PSVD, should the approach be the same as in adults?

Recommendation

- Diagnosis and management in children may follow the recommendations proposed for adults **(LoE 4, weak recommendation, consensus).**

Histopathological lesions compatible with PSVD have been described in children with cystic fibrosis and with syndromes such as Turner or Adams Oliver syndrome.[95,106,218] In addition, genetic mutations in *DGUOK, FOPV, FCHSD1, GIMAP5, HRG, KCNN3*, and *TRMT5* genes have been identified in children with both familial and non-familial PSVD.[218,231] Immunological/autoimmune disorders and malignancy have also been found associated with PSVD in children.[232,233]

Non-obstructive sinusoidal dilatation and peliosis hepatis

Non-obstructive sinusoidal dilatation (NO-SD) is defined as enlargement of the sinusoidal lumen (to more than one liver cell plate wide) in the absence of sinusoidal or post-sinusoidal obstruction.[234–236] Atrophy of hepatocytes and sinusoidal fibrosis can be present. The diagnosis of NO-SD requires exclusion of sinusoidal infiltration by sickle cells or neoplastic cells and hemophagocytic histiocytes, BCS or heart failure, small-for-size syndrome after LT, and SOS/VOD.[234–236]

The pathogenesis of NO-SD is unclear, but activation of the interleukin-6 and vascular endothelial growth factor pathways have been suggested to play a role.[234]

There are no specific signs or symptoms associated with NO-SD. Clinical presentation is variable, depending on the associated conditions. Liver enzyme abnormalities are frequent but not specific and include mild to moderate elevation of aminotransferases, alkaline phosphatases and/or gamma-glutamyltransferase; liver function is usually preserved.[234,235] Other laboratory abnormalities may be features of the associated disorders.

Peliosis hepatis is a rare vascular disorder characterised by blood-filled spaces distributed randomly throughout the liver parenchyma.[237,238] The size of the lesion may vary from 1 mm to several centimetres. Pathological distinction between parenchymal and phlebetactic types is obsolete. Peliosis hepatis usually involves the entire liver, but focal peliosis hepatis has been described. Peliosis hepatis may occur at any age, in both sexes.

Peliosis hepatis is often asymptomatic; however, it may be associated with rare, but severe complications, which include hepatic failure, portal hypertension, and liver rupture leading to haemoperitoneum and haemodynamic instability.[239]

In patients with liver-related abnormalities, which imaging features should raise a suspicion of non-obstructive sinusoidal dilatation and differentiate them from obstructive sinusoidal dilatation?

Recommendation

- Sinusoidal dilatation is suspected when CT and/or MRI show a “mosaic enhancement pattern” on late hepatic arterial phase or portal venous phase, that fades on delayed phase. Non-obstructive sinusoidal dilatation should be suspected in the absence of any cause of hepatic venous outflow obstruction, including Budd-Chiari syndrome, right heart failure or chronic pericarditis **(LoE 4, strong recommendation, strong consensus).**

A mosaic pattern is characterised by reticulated enhancement on contrast-enhanced acquisitions during the arterial-dominant and/or the portal venous phase that disappears during the delayed phase. On hepatobiliary phase, sinusoidal dilatation is characterised by a reticular hypointense appearance of the liver.[240,241]

Mosaic pattern enhancement is not specific to NO-SD.[242,243] It is observed in BCS as well as in any obstruction of venous outflow between the sinusoids and the heart, including pericardial diseases and heart failure. Moreover, a mosaic pattern can be seen in patients who underwent Fontan surgery and in SOS/VOD. The presence of imaging features related to outflow obstruction – such as hepatic venous occlusion, stagnant or reversed hepatic venous outflow, hepatic venous collaterals, or morphological changes of the liver – exclude the diagnosis of NO-SD.

If constrictive pericarditis is suspected, a haemodynamic study should be planned, which may show the so-called dip and plateau sign, consisting of an accentuated early dip in diastolic pressure followed by a plateauing in mid-late diastole.[244,245]

In patients suspected of having non-obstructive sinusoidal dilatation, is liver biopsy recommended to establish the diagnosis?

Recommendations

- In patients suspected of having non-obstructive sinusoidal dilatation based on imaging findings, liver biopsy is not systematically recommended to establish the diagnosis **(LoE 4, weak recommendation, consensus).**
- Liver biopsy can be considered when imaging findings persist 6 months after removing potential aetiological factors and/or are diffuse **(LoE 4, weak recommendation, consensus).**

Patients with NO-SD have variable and non-specific clinical presentation and liver blood test abnormalities.[234,235,246] In most published cases, diagnosis is based on histology and studies evaluating the diagnostic accuracy of imaging in comparison with histological examination are not available. Clinical outcomes of SD are mainly related to the associated disorders. In the study by Ronot *et al.*,[241] regression of NO-SD was observed in patients with marked systemic inflammatory syndrome once the extrahepatic condition had resolved. Resolution of clinical and radiological features has also been observed in cases associated with drug exposure.[247–250] Therefore, liver biopsy can be avoided at initial presentation but should then be considered if liver abnormalities persist. Liver biopsy can be performed through the percutaneous route with imaging guidance. However, the transjugular route may be preferable as it allows for HVPG measurement, the search for hepatic vein-to-vein communications suggestive of PSVD, and right heart catheterisation including the search for the dip and plateau sign.[245]

In patients with non-obstructive sinusoidal dilatation, what work-up should be carried out to identify associated conditions?

Recommendation

- Work-up aimed at detecting associated conditions should include, depending on the clinical context **(LoE 4, strong recommendation, strong consensus):**
  - History of drug use (including oral contraceptive use)
  - Screening for solid tumours
  - Screening for bacterial infections (*e.g.* pyelonephritis)
  - Screening for myeloid or lymphoproliferative disorders, including Castleman disease
  - Testing for HIV infection
  - Screening for antiphospholipid antibody syndrome
  - Screening for inflammatory bowel disease and for connective tissue disorders

Hepatic NO-SD is associated with several disorders,[234–236,246,251] which may involve decreased portal venous inflow or systemic inflammatory reaction syndrome. However, in some patients SD remains an isolated and unexplained finding.

Drugs are commonly associated with NO-SD, including: (i) chemotherapy, particularly platinum-based chemotherapy;[252–255] (ii) azathioprine,[256,257] mainly in the setting of kidney transplantation; and (iii) long-term use of oral contraceptives,[247,248,250,258–260] with lesions predominating in the periportal and midzones that may be accompanied by mild sinusoidal fibrosis. However, the role of oral contraceptives as a cause of SD is controversial, as no large study has clearly shown a link between both entities. In addition, the association between chronic oral contraceptive use and NO-SD was identified in years when the oestrogen content of oral contraceptives was high. The association between pregnancy and NO-SD is anecdotal.

Sinusoidal dilatation can also be viewed as a feature of idiopathic non-cirrhotic portal hypertension/PSVD, as 95% of patients with idiopathic non-cirrhotic portal hypertension show some sinusoidal dilatation on their biopsies,[106,209,261] either as an isolated finding or associated with other characteristic vascular abnormalities. Other vascular disorders associated with SD include extrahepatic portal vein thrombosis, congenital portacaval shunts, Abernethy malformation, and Fontan-associated liver disease.[246,262]

In patients with non-obstructive sinusoidal dilatation, which follow-up modalities should be implemented to improve patient outcomes?

Statement

- There is currently no data on the long-term outcomes of patients with non-obstructive sinusoidal dilatation **(LoE 5, strong consensus).**

Recommendation

- Follow-up including liver blood tests and imaging may be proposed. First follow-up may be 6 months to 1 year after initial diagnosis, with subsequent follow-up visits at longer intervals, if liver status remains stable **(LoE 5, weak recommendation, strong consensus).**

The natural history of NO-SD is mostly unknown. Few retrospective follow-up data are available, which indicate that patient outcomes are mainly related to the associated conditions rather than to the NO-SD itself.[241,246,263]

In patients with drug-related non-obstructive sinusoidal dilatation, is drug discontinuation recommended to improve outcomes?

Recommendations

- In patients with non-obstructive sinusoidal dilatation receiving platinum-based chemotherapy, discontinuation of this therapy is not recommended **(LoE 3, strong recommendation, strong consensus).**

- In patients with non-obstructive sinusoidal dilatation receiving oral contraceptives, discontinuation of this therapy may be considered to reverse sinusoidal dilatation **(LoE 4, strong recommendation, strong consensus).**

There is no evidence that oxaliplatin associated NO-SD affects post-operative outcome. In a study by Mehta *et al.* on patients undergoing liver resection for colorectal liver metastases,[252] the prevalence of SD was significantly higher in the oxaliplatin group compared to the other groups, but it did not increase postoperative morbidity or mortality. In the study by Aloia *et al.*,[253] centrilobular necrosis and nodular regenerative hyperplasia, but not SD, were associated with increased intraoperative transfusion requirements.

The clinical significance of SD in the setting of oral contraceptives is not clear. However, reported cases demonstrated that clinical symptoms, liver function abnormalities, and imaging findings may resolve after stopping oral contraceptives.[248–250,264] In the study by Ronot *et al.*,[241] the two patients with persistent mosaic enhancement at follow-up were on oral contraceptives and had no persistent infection or inflammation. However, clinical outcome was uneventful despite oral contraception not being discontinued.

In patients with liver abnormalities, which features are needed to make a diagnosis of peliosis hepatis?

Statement

- There are no specific imaging features for peliosis hepatis **(LoE 4, strong consensus).**

Recommendation

- Peliosis hepatis should be suspected in the case of focal lesions mimicking tumours, particularly in the case of strong hyperintensity on T2 and persistent enhancement on CT/MRI during delayed phase. Diagnosis of peliosis hepatis requires a liver biopsy showing blood-filled spaces not entirely lined with endothelial cells. Reticulin fibres may be absent **(LoE 4, strong recommendation, strong consensus).**

Peliosis hepatis presents a broad spectrum of imaging findings. Most literature consists of case reports, and very few papers systematically describe the different imaging features.[265,266] On imaging, peliosis hepatis may be misdiagnosed as benign or malignant focal liver lesions.[267,268] Indeed, in terms of differential diagnosis, peliosis hepatis is considered a great mimic. Characteristic imaging features are summarised in Table 8.

In patients with peliosis hepatis, which management modalities should be applied to improve patient outcomes?

Recommendations

- Predisposing conditions should be removed when feasible **(LoE 4, strong recommendation, strong consensus).**
- MRI is suggested to monitor disease progression. First follow-up may be 6 months to 1 year after initial diagnosis, with subsequent follow-up visits at longer intervals, if liver status remains stable **(LoE 5, weak recommendation, strong consensus).**
- In patients with peliosis hepatis and suspicion of complications, CT or MRI is suggested to diagnose haemorrhage. Management of haemorrhage should be discussed with expert centres considering simple surveillance, interventional radiology and surgery **(LoE 5, weak recommendation, strong consensus).**

In adults, potential associated factors include transplantation,[269] haematologic malignancy, infections (tuberculosis, HIV), and drugs including chemotherapeutic agents, anabolic steroids, and oral contraceptives.[238,269–271] The term "bacillary" peliosis hepatis refers to a well-recognised manifestation of disseminated *Bartonella henselae* infection that can occur in immunocompromised individuals.[272]

The progression of peliosis hepatis is still uncertain. The development of serious complications, including intraperitoneal haemorrhage, has been reported, justifying the need to monitor the disease. Surgical resection may be considered, particularly in pseudotumoral cases and when imaging studies show worsening of the lesions.

Currently, there is no specific treatment for peliosis hepatis, with treatment varying from case to case. If the condition

Table 8. Imaging features of peliosis hepatis and differential diagnoses.

Diagnostic test	Features
Ultrasound	Hypoechoic/hyperechoic lesions, often multiple; heterogeneous if complicated by haemorrhage. Doppler studies can show both perinodular and intranodular vascularity.
CT/MRI dynamics	On unenhanced CT, multiple areas of low attenuation. On contrast-enhanced CT or MRI, enhancement is variable. Classical presentation is hyperenhancement to liver parenchyma on hepatic arterial phase which becomes progressively isodense/intense with time. No wash-out is seen on delayed phase, contrast uptake may be seen. No mass effect on hepatic vessels is usually observed. Haemorrhage may be seen.
MRI	On T2-weighted sequences, peliotic lesions are usually hyperintense to liver parenchyma.
Angiography	Peliotic lesions appear as multiple vascular nodules during the late arterial phase. The enhancement of peliotic lesions is typically more distinct during the parenchymal phase and persists during the portal venous phase.

appears to be related to a medical therapy, the medication can be stopped. Patients with bacillary peliosis hepatis or with disseminated tuberculosis have demonstrated a response to specific antibiotic therapy.

In children with non-obstructive sinusoidal dilatation or peliosis hepatis, should management be the same as in adults?

Recommendation

- Management in children should follow the adult recommendations **(LoE 4, strong recommendation, consensus).**

Although extremely rare, both NO-SD and peliosis hepatis should be considered in children in the appropriate clinical setting.

Although there are no reported cases of NO-SD in children, hepatotoxic agents used in adult patients are also used in paediatrics. In addition, the systemic diseases associated with NO-SD in adults also occur in children. Therefore, should a case compatible with NO-SD present in children, it is reasonable to rely on evidence in adult patients for management.

Peliosis hepatis in children is mostly associated with chronic conditions, including cystic fibrosis, malnutrition, Fanconi anaemia, adrenal tumours, Marfan's syndrome, congenital cardiopathy, and myotubular myopathy, or it can occur following renal transplantation.[273,274] Peliosis hepatis in children without underlying pathologic conditions is very rare; only a few cases have been reported in the literature.

Clinical manifestations of peliosis hepatis in children may include acute liver dysfunction, hepatomegaly, and suggestive imaging. Although mortality is reportedly high, maximal medical and surgical management may be life-saving.[273,275]

Sinusoidal obstruction syndrome

Haematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for many patients with haematological malignancies; however, conditioning regimens necessary to eradicate the underlying disease may cause endothelial cell activation and injury, resulting in sinusoidal obstruction syndrome (SOS), also referred to as veno-occlusive disease.

Liver SOS is a potentially life-threatening complication of HSCT. The most severe form of the disease is associated with multiorgan dysfunction and failure and a mortality rate of >80% in untreated patients. Risk factors for SOS include very young age (<2 years), previous hepatic disease, previous treatment with gemtuzumab ozogamicin or inotuzumab ozogamicin, high-intensity or myeloablative conditioning regimens (in particular patients who received busulfan), and previous exposure to sirolimus.[276] Diseases particularly associated with severe SOS after HSCT include haemophagocytic lymphohistiocytosis, thalassaemia with liver fibrosis, neuroblastoma, and osteopetrosis. The incidence of SOS after HSCT has been reported to be as high as 60% in very high-risk populations, but its incidence is significantly influenced by patient characteristics, conditioning regimens, and transplantation type (allogeneic *vs*. autologous; mismatched unrelated donors) and is now much lower at around 2%.[277]

SOS occurs as a result of activation and damage of the sinusoidal endothelium. In the HSCT setting (allo- or auto-HSCT), endothelial damage initially caused by radiation or toxic metabolites of conditioning regimens can be exacerbated by proinflammatory and proapoptotic responses of the endothelial tissues. The synthesis of clotting factors facilitates platelet aggregation, leading to a hypercoagulable state.[278]

In patients undergoing HSCT, what prophylaxis should be used to decrease the incidence of sinusoidal obstruction syndrome?

Recommendations

- Prophylaxis with ursodeoxycholic acid is recommended in all patients to decrease the incidence of sinusoidal obstruction syndrome **(LoE 1, strong recommendation, consensus).**
- Defibrotide prophylaxis is generally not recommended to prevent sinusoidal obstructive syndrome **(LoE 2, strong recommendation, consensus).**

Prophylaxis of SOS following HSCT includes reducing SOS modifiable risk factors.[276] These risk factors are: (i) conditioning regimens including high-dose (myeloablative) regimens, oral or high dose busulfan, high-dose treosulfan and high-dose total body irradiation-based regimen; (ii) unrelated donors or HLA-mismatched donors; (iii) GVHD prophylaxis based on sirolimus + methotrexate+ tacrolimus, methotrexate + cyclosporin or tacrolimus, or non T cell-depleted transplant; (iv) use of parenteral nutrition.[276]

The use of ursodeoxycholic acid for SOS prophylaxis has been tested in three randomised trials. Two of them[279,280] demonstrated a significant reduction in the incidence of SOS in the ursodeoxycholic acid arm, but one reported no difference.[281] A systematic review[282] reported a benefit of using ursodeoxycholic acid in terms of transplant-related death and a Cochrane meta-analysis[283] showed a reduction of both SOS-related and all-cause mortality.

The suggested dose is 12 to 15 mg/kg divided into two doses starting the day before conditioning and continuing for 3 months after HSCT.

Defibrotide has been shown to stabilise and protect endothelial cells *in vitro* through restoration of the thrombotic–fibrinolytic balance. Defibrotide also exerts anti-inflammatory and antioxidant effects and has anti-apoptotic and anti-angiogenic properties, suggesting potential use as a prophylactic drug for SOS. Several studies of defibrotide for SOS prophylaxis in patients at high risk for the disease have been reported. A large phase III, prospective RCT (NCT00272948) in paediatric patients (<18 years) at high risk for the disease showed a lower incidence of SOS at day 30 after HSCT with defibrotide prophylaxis (at 12%) *vs*. control (no defibrotide; 20%) ($p = 0.0507$).[284] A meta-analysis of >1,000 patients from RCTs and retrospective analyses suggested a reduction in the

Table 9. SOS criteria for diagnosis (adults) adapted from EBMT 2023 criteria.[276]

Degree of certainty of SOS diagnosis		
Probable	**Clinical**	**Proven**
Two of the following criteria must be present: Bilirubin ≥2 mg/dl Painful hepatomegaly Weight gain >5% Ascites Ultrasound and/or elastography suggestive of SOS	Bilirubin ≥2 mg/dl and two of the following criteria must be present: Painful hepatomegaly Weight gain >5% Ascites	Histologically proven SOS
Onset		
In the first 21 days after HSCT: *classical SOS*	>21 days after HSCT: *late-onset SOS*	

EBMT, European Society for Blood and Marrow Transplantation; HSCT, haematopoietic stem cell transplantation; HVPG, hepatic venous pressure gradient; SOS, sinusoidal obstruction syndrome.
Contrary to EBMT 2023 criteria,[276] we consider that HVPG ≥10 mmHg reinforces clinical suspicion, but is not sufficient for a proven SOS diagnosis.[303] For any patient, these symptoms/signs should not be attributable to other causes.

risk of SOS for patients treated with defibrotide prophylaxis *vs.* controls (risk ratio 0.3; 95% CI 0.12–0.71; p = 0.006), suggesting a benefit of defibrotide prophylaxis.[285] A large, retrospective study (n = 248) also supported a benefit of defibrotide prophylaxis on the incidence of SOS at day 100.[286]

However, the recent HARMONY, randomised, multicentre, phase III trial, including 372 patients at high risk or very high risk of developing SOS gave opposite results. The primary endpoint was SOS-free survival at day 30 after HSCT. At the final analysis, SOS-free survival by day 30 after HSCT was 67% (95% CI 58-74) in the defibrotide prophylaxis group and 73% (62-80) in the best supportive care group (HR 1.27; 95% CI 0.84-1.93; p = 0.85).[287] This observation was similar across age groups. Based on these data, defibrotide is not recommended to prevent SOS.

Other strategies proposed include recombinant thrombomodulin, an endothelial anticoagulant co-factor, as prophylactic therapy may be able to prevent veno-occlusive complications after stem cell transplantation.[288] However, data are currently insufficient to recommend its use and RCTs are needed.

Heparins have previously been used for SOS prophylaxis. However, a large meta-analysis reported that the use of unfractionated heparin or LMWH prophylaxis was not associated with a significant decrease in the risk of SOS (pooled RR 0.90; 95% CI 0.62–1.29).[289] Furthermore, bleeding was reported as an adverse event in 7 of the 12 studies in the meta-analysis (2,782 patients).[289] Therefore, given the absence of conclusive results on its effectiveness and its potential side effects, heparins are not part of the recommended prophylaxis for SOS.

A recent network meta-analysis of RCTs allowed the efficacy of different primary prophylaxis strategies to be assessed using a cumulative ranking probability index and confirmed that ursodeoxycholic acid ranked first in terms of efficacy.[290]

In patients with liver abnormalities following HSCT, what features should raise a suspicion of sinusoidal obstruction syndrome over other liver diseases?

Recommendation

- The following signs should raise suspicion of sinusoidal obstruction syndrome: (i) clinical manifestations including hepatomegaly, hepatalgia, fluid retention with ascites, weight gain, transfusion refractory thrombocytopenia, jaundice; (ii) elevated LSM; (iii) ultrasound findings including hepatomegaly, gallbladder wall thickening, signs of portal hypertension (splenomegaly, ascites, decrease in velocity or reversal of the portal venous flow); and (iv) contrast-enhanced CT or MRI findings showing mosaic enhancement pattern on late arterial phase or on portal venous phase. Signs typically occur within 21 days after HSCT, but late-onset sinusoidal obstruction syndrome is possible after this time interval **(LoE 3, strong recommendation, strong consensus).**

Clinical manifestations of SOS following HSCT include hepatomegaly, hepatalgia, fluid retention with ascites, weight gain, transfusion refractory thrombocytopenia and jaundice.[276]

Ultrasound in SOS following HSCT can detect non-specific abnormalities including (i) hepatomegaly, (ii) splenomegaly, (iii) gall bladder wall thickening, (iv) dilatation of the main portal vein, (v) ascites, (vi) paraumbilical vein visualisation, (vii) decreased mean velocity of the portal vein, (viii) hepatofugal flow or no flow in portal vein, and (ix) hepatic artery resistive index ≥0.75 [291]. A decrease in velocity or reversal of the portal venous flow and paraumbilical vein visualisation are considered more specific for SOS, but are inconsistent and usually occur late in the disease.[292–296] There are currently no early ultrasound-specific signs that can discriminate the various hepatic complications following HSCT.[291,295] Pitfalls associated with ultrasound and Doppler include heterogeneity and lack of reproducibility and the late onset of some radiological signs (*e.g.* reverse flow in the portal vein) that can occur in SOS. In a study of 106 patients who underwent alloHSCT, including 10 (9.4%) diagnosed with SOS according to Baltimore or Seattle criteria, an ultrasound score, HokUS-10, was established, consisting of 10 parameters, later refined to only six.[296,297] The sensitivity and specificity were 95% and 97%, respectively. However, the endpoint used to construct this score was only a clinical diagnosis of SOS and not a proven diagnosis of SOS, so the added value of this score over clinical criteria is unclear (Table 9). Moreover, independent validation is still needed, ideally using proven SOS as an endpoint.

LSM has been proposed as a marker of SOS. Colecchia *et al.* used transient elastography to evaluate LSM in a cohort of 78 patients before alloHSCT and at days +9/10, +15/17, and +22/24 after alloHSCT.[298] Four patients developed SOS at a median time of +17 days after alloHSCT and a sudden increase in LSM, compared with previously assessed values and

Table 10. Severity grading of SOS in adults adapted from EBMT 2023 criteria.[276]

	Mild *	Moderate *	Severe	Very severe – MOD **
Time since clinical symptoms of SOS	>7 days	5–7 days	≤4 days	Any time
Bilirubin (mg/dl)	≥2 and <3	≥3 and <5	≥5 and <8	≥8
Bilirubin kinetic			Doubling within 48 h	
Transaminases	≤2x normal	>2 and ≤5x normal	>5 and ≤8x normal	>8x normal
Weight increase			≥5%	≥10%
Renal function (creatininemia)	Baseline at transplant	<1.5x baseline at transplant	≥1.5 and <2x baseline at transplant	≥2x baseline at transplant or diagnosis of MOD **

MOD, multiple organ dysfunction; SOS, sinusoidal obstruction syndrome.
Patients belong to the category that fulfilled ≥2 criteria. If patients fulfilled ≥2 criteria in two different categories, they must be classified in the more severe category.
*In case of presence of ≥2 risk factors for SOS, patients should be in the upper grade (see risk factors in EBMT 2023.[276]
**Patients with MOD must be classified as very severe. MOD is defined as ≥2 organs from the SOFA score with a score ≥2, or an increase ≥2 of organ dysfunction for patients with underlying organ involvement (see in EBMT 2023[276]).

pre-HSCT values, was seen in all patients who developed SOS. These findings were confirmed by a French group that performed transient elastography and 2D-shear wave elastography (2D-SWE) before alloHSCT, at day +7 and day +14 in 146 patients.[295] They found that a 2D-SWE at day +14 >8.1 kPa allowed for early detection of SOS (AUC = 0.84, $p = 0.004$), with a high sensitivity (75%) and specificity (99%). Importantly, this study used proven SOS as an endpoint. Moreover, the authors showed that 2D-SWE improved the specificity of the Seattle, Baltimore or European Society for Blood and Marrow Transplantation (EBMT) scores for SOS. In a large Italian study including 941 patients (774 adults and 167 children) who underwent LSM and HSCT, a stepwise algorithm combining the rule-in (25 kPa) and rule-out (6 kPa) cut-offs with a delta LSM (×2) achieved high positive (96%) and negative (97.5%) predictive values.[299]

The use of other imaging techniques, including CT and MRI, have been investigated in SOS in the setting of HSCT with no specific findings.[291,300]

In patients suspected of having sinusoidal obstruction syndrome following HSCT, how should the diagnosis be established?

Recommendation

- Criteria adjusted from EBMT 2023 should be used to diagnose sinusoidal obstruction syndrome, considering three degrees of certainty: probable, clinical and histologically proven (Table 9) **(LoE 3, strong recommendation, strong consensus).**

For a long time, two definitions of SOS have coexisted, based on the Seattle criteria, reported by McDonald *et al.*,[301] and the Baltimore criteria, reported by Jones *et al.*.[302] While these definitions were used in clinical practice and in research studies, they were not suitable for early diagnosis and they missed late-onset SOS. Therefore, EBMT criteria for SOS were published in 2016 and revised in 2023 (Table 9).[276] They distinguish classical from late-onset SOS (beyond day 21). They also identify three degrees of diagnosis with increasing confidence: probable, clinical and proven. For the sake of homogeneity, the present EASL guidelines recommend following the EBMT 2023 criteria, with one caveat, *i.e.* the use of HVPG to consider a diagnosis of proven SOS.[276] Indeed, even though HVPG is higher in patients with SOS than in those without, low HVPG values do not rule out SOS.[303] Moreover, in a study gathering 77 patients with a clinical suspicion of SOS and a liver biopsy available, HVPG >10 mmHg has a specificity of only 78% and a positive predictive value of 66% for the diagnosis of SOS.[303] We thus think that the term "proven SOS" should be restricted to histologically proven SOS. As haemostasis is often impaired in patients with clinical suspicion of SOS, the transjugular route should be used as it is safe.[303,304]

Severity of SOS can be graded according to EBMT 2023 criteria (Table 10). However, we would like to point out that classifying patients in the upper grade when they have ≥2 risk factors for SOS is debatable and will need to be refined in the future.[276]

In patients with sinusoidal obstruction syndrome following HSCT, which treatments can be considered to reduce morbidity and mortality?

Recommendations

- Defibrotide is recommended when SOS is severe to improve survival **(LoE 3, strong recommendation, strong consensus)**, and can be considered when sinusoidal obstruction syndrome is moderate **(LoE 3, weak recommendation, consensus).** Early initiation after the diagnosis of sinusoidal obstruction syndrome may be preferable **(LoE 3, weak recommendation, strong consensus).**

- In patients with severe or very severe sinusoidal obstruction syndrome following HSCT, TIPS may be considered in case of rapid clinical deterioration despite medical treatment, including defibrotide, to improve outcomes **(LoE 4, weak recommendation, consensus).**

- In patients with very severe sinusoidal obstruction syndrome following HSCT, LT may be discussed in patients with a favourable haematological prognosis **(LoE 5, weak recommendation, strong consensus).**

Defibrotide is approved for the treatment of SOS with renal or pulmonary dysfunction after HSCT in the USA and severe hepatic SOS after HSCT in patients older than 1 month in the EU. These approvals are mainly based on a pivotal multicentre phase III trial that assessed the effect of a 25 mg/kg/day dose in 102 patients (median age 21 years, range 0–72) with severe SOS/VOD.[305] Randomisation to placebo or supportive care was deemed unethical. Therefore, a historical control group (n = 32) was used in this trial, screened among almost 7,000 sequential patients. Treatment with defibrotide was associated with a significantly higher complete remission rate (24 *vs.* 9%, $p = 0.013$) and day +100 overall survival (38 *vs*. 25%, $p = 0.034$). No differences in adverse event incidence were reported between the two groups, including for haemorrhagic toxicity (65% *vs.* 69%).[305] Defibrotide should be initiated as soon as possible in those patients, as earlier defibrotide initiation has been associated with higher day +100 overall survival.[306]

Furthermore, given that early treatment initiation is associated with a higher day +100 overall survival, and that moderate SOS/VOD is associated with significant mortality,[306] early initiation of defibrotide in patients with moderate SOS can also be considered.[276] For patients with mild SOS, supportive care must be pursued with close monitoring of severity criteria to allow for early initiation of defibrotide in case of worsening. Defibrotide is administered at a dose of 25 mg/kg/day for at least 14–21 days, and until resolution of SOS.[276]

Initial experience with TIPS performed for treatment failure in patients with SOS, published in case reports or very small case series, reported some success in portal decompression, but no positive impact on overall survival.[307,308] Therefore, previous guidelines recommended against its use in SOS.[95,309,310] Recently, positive experiences with TIPS have been reported.[311–313] In particular, a retrospective study described the outcome of seven patients with very severe SOS treated with TIPS, a median of 4 days after SOS diagnosis (range, 1 to 28 days), owing to rapid clinical deterioration despite medical treatment, including defibrotide. Following TIPS insertion, all patients showed clinical improvement with hepatomegaly, ascites, and renal failure resolution, and all showed analytical improvement with reduced ALT, creatinine, and INR values, except for patient 2, whose indication for TIPS was refractory hepatorenal syndrome with a normal ALT level. All patients met the criteria for complete remission at a median of 8 days after TIPS insertion. The 100-day overall survival was 100%.[311] Even if more data are needed, these results suggest that TIPS should be promptly considered (*i.e.* within a few days) in rapidly progressive cases despite medical treatment, including defibrotide.

Cases of LT in patients with severe SOS have been reported.[314–316] However, LT is limited by the underlying malignancy, which may itself be a contraindication, and should only be proposed in patients with a favourable oncological prognosis or non-oncological aetiology.

In patients with sinusoidal obstruction syndrome following HSCT, what long-term follow-up should be proposed to improve patient outcomes?

Statement

- Patients with sinusoidal obstruction syndrome following HSCT can develop intrahepatic non-cirrhotic portal hypertension in the long-term **(LoE 5, strong consensus).**

Recommendation

- Follow-up including liver blood tests and imaging may be considered. First follow-up may be 3 to 6 months after initial diagnosis, with subsequent follow-up visits at longer intervals, if liver status remains stable **(LoE 5, weak recommendation, strong consensus).**

Data on long-term outcomes of SOS are limited. One retrospective study reported the outcome of 23 patients with histologically proven SOS who survived ≥6 months after HSCT. After a median follow-up of 6.1 years (IQR 2.4–8) after SOS, 10 (44%) patients developed signs of portal hypertension (portosystemic collaterals n = 10; oesophageal varices, n = 6; portal vein thrombosis, n = 1), and eight of them liver-related events (ascites n = 8; spontaneous bacterial peritonitis, n = 1; hepatic encephalopathy, n = 3; variceal bleeding, n = 3), a median of 1.3 years (IQR 0.89–4.17) after SOS. The cumulative incidence of signs of portal hypertension was 50%, 60%, and 90% at 1, 3, and 10 years, respectively. Cumulative incidence of liver-related events was 30%, 60%, and 80% at 1, 3 and 10 years, respectively. Out of the 10 patients who developed signs of portal hypertension during follow-up, three underwent a second liver biopsy 1.3 (IQR 1.0–2.7) years after SOS diagnosis, and all biopsies showed features of PSVD; six additional patients underwent LSM showing values ranging from 6 to 15 kPa (median 13 kPa). Cumulative incidence of death was significantly higher in patients who developed signs of portal hypertension than in those who did not (HR 10.9; 1.3–91.7; $p = 0.028$).[317] These limited data suggest that patients with SOS are at risk of developing intrahepatic non-cirrhotic portal hypertension in the long term, so screening for these signs may help guide appropriate prophylaxis for variceal bleeding.

In patients with liver abnormalities outside the HSCT setting, which features should raise a suspicion of sinusoidal obstruction syndrome over other liver diseases?

Recommendations

- In patients receiving oxaliplatin-based chemotherapy, or other drugs less commonly associated with sinusoidal obstruction syndrome development (Box 1), the following signs should raise a suspicion of SOS: contrast-enhanced CT or MRI showing perfusion abnormalities including mosaic enhancement pattern on late arterial phase or on portal venous phase, development of signs of portal hypertension, liver blood test abnormalities **(LoE 4, strong recommendation, strong consensus).**

- As these signs are not specific, liver biopsy is recommended to make a diagnosis of sinusoidal obstruction syndrome in this setting **(LoE 4, strong recommendation, strong consensus).**

Outside the HSCT setting, oxaliplatin is the most well-described drug associated with SOS development.[318]

In the short term, oxaliplatin-based chemotherapy is a major cause of SOS. Oxaliplatin-associated SOS was first reported in 2004 in a histopathological analysis of 87 post-chemotherapy liver resection specimens, which revealed that 44 (51%) had sinusoidal dilatation and haemorrhage, related to rupture of the sinusoidal barrier; sinusoidal changes were strongly associated with the use of oxaliplatin, occurring in 34 out of 43 patients treated with this drug (78%).[319] Sinusoidal injury associated with oxaliplatin occurs without significant serum enzyme elevations or clinically apparent liver injury in the majority of cases. APRI (aspartate aminotransferase-to-platelet ratio index) score was identified as independently associated with severe SOS after oxaliplatin therapy.[320] An APRI score >0.36 had the best accuracy for estimating the presence of high grade SOS, with an AUC of 0.85, a sensitivity of 87% and a specificity of 69%.[320] At imaging, liver perfusion heterogeneity is very common, observed in 60–90% of patients treated with oxaliplatin-based regimens.[321,322] Splenomegaly is also common, as observed in 86% of patients receiving oxaliplatin-containing adjuvant therapy in another retrospective study. Increase in spleen size correlated with the cumulative oxaliplatin dose and with higher histologic grades of sinusoidal injury in the multivariate analysis.[323] Clinical consequences of sinusoidal injury caused by oxaliplatin include, in the short term, a decrease of hepatic functional reserve with higher postoperative values of total bilirubin, and longer hospital stay.[324] In a retrospective analysis of resected liver specimens from patients in two prospective non-randomised trials (5-fluorouracil/oxaliplatin ± bevacizumab) it was evident that bevacizumab protected against the development of SOS via an unknown mechanism.[325] Currently, there are no approved drugs for the prevention or treatment of oxaliplatin-associated SOS.[326]

Box 1. Drugs known to cause sinusoidal obstruction syndrome.

- Actinomycin D
- Azathioprine
- Busulfan
- Carmustine
- Cytosine arabinoside
- Cyclophosphamide
- Dacarbazine
- Gemtuzumab-ozogamicin
- Immune check-point inhibitors
- Melphalan
- Mercaptopurine
- Mitomycin
- Mycophenolate mofetil
- Oxaliplatin
- Pyrrozolidine alkaloids
- Urethane
- Tacrolimus
- Terbinafine
- Traditional herbal remedies
- 6-mercaptopurine
- 6-thioguanine
- Total-body irradiation
- Hepatic irradiation (high doses)
- Platelet transfusion containing ABO-incompatible plasma

In the long term, oxaliplatin-based chemotherapy can lead to PSVD with portal hypertension and its complications, namely variceal bleeding and ascites.[321,327,328] The incidence of chronic (non-reversible) portal hypertension-related to oxaliplatin has been estimated in a large retrospective cohort study of 356 patients with a mean follow-up of approximately 5 years (range: 0.2–8.1 years).[329] Imaging findings of portal hypertension persisted and progressed until the last follow-up in 1.4% of patients (5/356).[329]

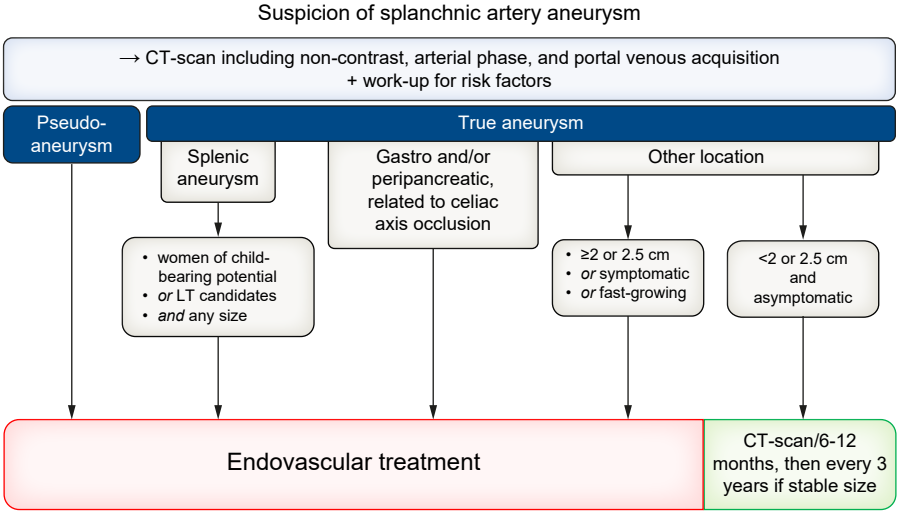

Fig. 4. Difference between true aneurysms and pseudoaneurysms.

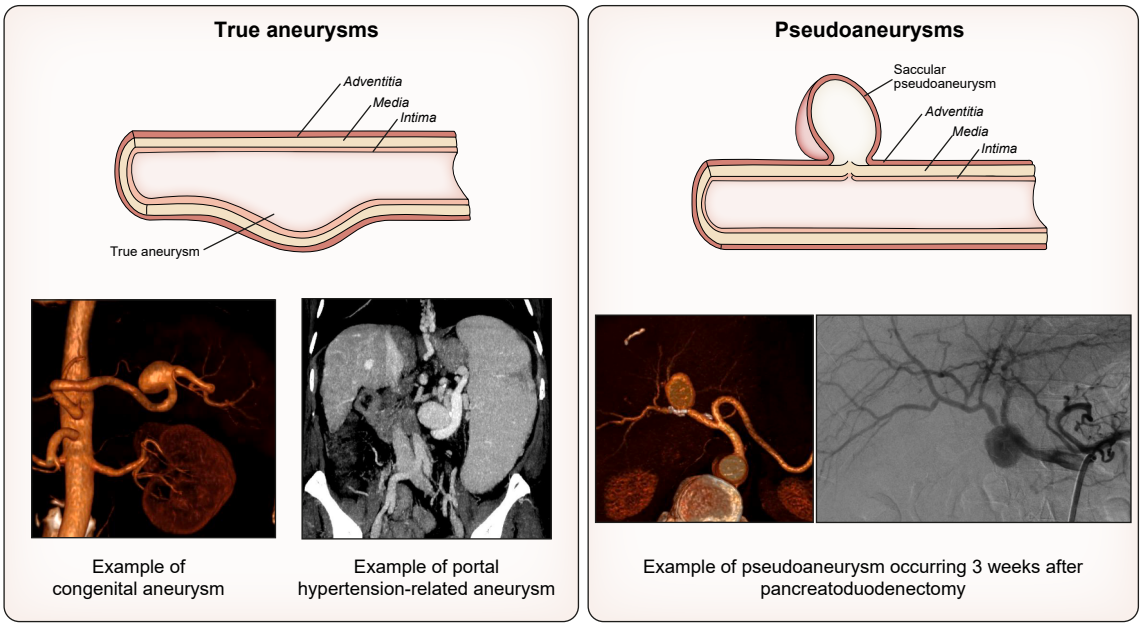

Fig. 5. Management of splanchnic artery aneurysms. LT, liver transplantation.

Other drugs have been reported as a cause of SOS and are listed in Box 1.[310,318,330,331] Pyrrolizidine alkaloids, found in plants or bushes from which tea is made or that contaminate seeds, are well-documented causes of SOS, but are not addressed in the present guidelines, since they are extremely rarely encountered in Western countries.[332,333]

In patients with sinusoidal obstruction syndrome outside the HSCT setting, which treatment modalities should be used to improve patient outcomes?

Recommendations

- Drugs associated with sinusoidal obstruction syndrome development should be stopped whenever possible. No recommendation can be made in favour or against the use of defibrotide in this setting **(LoE 5, weak recommendation, strong consensus).**
- TIPS may be considered in cases of severe complications of portal hypertension **(LoE 5, weak recommendation, consensus).**

Outside the HSCT setting, in patients with drug-associated SOS, imaging and clinical signs of SOS may resolve when the drug is withdrawn. For example, in a large retrospective cohort study of 356 patients receiving oxaliplatin-based therapy with a mean follow-up of approximately 5 years (range: 0.2–8.1 years),[329] 90% of the patients developed parenchymal heterogeneity (grade 2 or higher) on abdominal CT scans, which was not present before treatment and was used as a surrogate for vascular changes. These changes were reversed in 68% of patients after 1 year.[329]

Other drugs, such as tacrolimus and mycophenolate mofetil, have been associated with SOS and their replacement with other immunosuppressive agents has been associated with resolution of imaging and clinical signs of SOS.[330,331]

Outside the HSCT setting, off-label use of defibrotide has been described.[318] Reported results seemed favourable, but the heterogeneity of the data precludes firm conclusions.[318]

Outside the HSCT setting, experience with TIPS for SOS is very limited. Most data have been reported in patients with SOS caused by pyrrolizidine alkaloids.[334–336]

Whether these data can be extrapolated to other causes of SOS remains unknown.

In children suspected of having sinusoidal obstruction syndrome, should the approach be the same as in adults?

Recommendation

- In contrast to adults, defibrotide should be initiated as soon as sinusoidal obstruction syndrome is suspected in children, regardless of severity, as this treatment may improve outcomes **(LoE 4, strong recommendation, consensus).**

In children, the mortality rate from SOS is 80%. Its incidence is on the rise given the increase in therapeutic modalities for haematological malignancies and indications for HSCT.[337,338] Risk factors for SOS in children include osteopetrosis, neuroblastoma (high-risk), thalassemia, and congenital haemophagocytocytic syndromes.[284,339–341] Children <12 months of age appear to be uniquely vulnerable with

as many as 30% of infants developing SOS in this age group in the oncological setting.[284,342] Although severity criteria have been established,[343] it is generally accepted that the diagnosis is clinical, regardless of meeting some or all diagnostic criteria.[344] Akin to what is accepted in adults, ursodeoxycholic acid is the main prophylactic treatment at this time.[281] Regarding defibrotide as a prophylactic treatment, a phase III study of defibrotide prophylaxis in paediatric patients at a high risk of SOS reported that SOS incidence at day 30 after HSCT was lower with defibrotide prophylaxis (12%) *vs.* controls (20%; risk difference −7.7%; 95% CI −15.3 to −0.1; $p = 0{\cdot}0507$).[284] However, these results were not confirmed in the recent HARMONY, randomised, multicentre, phase III trial, including 198 patients aged ≤16, at high risk or very high risk of developing SOS. SOS-free survival by day 30 after HSCT was not different between the defibrotide prophylaxis group and the best supportive care group.[287]

A recent retrospective study including 111 paediatric patients showed that early initiation of defibrotide, as soon as two EBMT diagnostic criteria are met, was associated with decreased severity of SOS and improved outcomes after SOS.[338]

Aneurysms of splanchnic arteries

Splanchnic artery aneurysms (SAAs) are a type of visceral artery aneurysm. They comprise aneurysms developed in the celiac trunk and tributaries (hepatic artery, splenic artery, pancreaticoduodenal and gastroduodenal arteries, gastric and gastroepiploic arteries) and in the superior or inferior mesenteric artery. They are rare vascular diseases, with renal artery aneurysm – defined as a visceral and not a splanchnic aneurysm – being the more common location.[345] In a systematic review, the most common sites of SAAs were the splenic artery followed by the hepatic artery, pancreaticoduodenal and gastroduodenal arteries, superior mesenteric artery, celiac artery, and others.[345]

SAAs should be further divided into true aneurysms and pseudoaneurysms (Fig. 4). True aneurysms are mostly related to degeneration or atherosclerosis. Yet, the presence of multiple aneurysms should raise the possibility of arterial or inherited diseases, the most common being connective tissue disorders (*e.g.* Marfan's, Ehlers-Danlos, fibromuscular dysplasia) or vasculitis.[346] On the contrary, splanchnic artery pseudoaneurysms are mostly related to trauma, iatrogenic injury, local inflammatory processes, or infection.[346] There are differences between true and pseudoaneurysm. In a true aneurysm, the aneurysm is bound by all three layers of the vessel wall (intima, media and adventitia) while a pseudoaneurysm occurs when a blood vessel wall is injured. Blood leaking from the vessel collects in surrounding tissue.

In the past, most SAAs were diagnosed in symptomatic patients, but now they are often diagnosed incidentally on imaging, especially CT.

The diagnosis of an aneurysm is based on a focal dilatation of the artery (Fig. 4). The differentiation between a true aneurysm and a pseudoaneurysm relies on the clinical context and imaging findings. A history of trauma, intervention, or infection favours the diagnosis of a pseudoaneurysm. A regular arterial dilatation is commonly seen in true aneurysm, while focal arterial disruption and inflammatory changes around an irregular aneurysm sac suggest the diagnosis of a pseudoaneurysm.[347] Pseudoaneurysms are also more likely to be diagnosed as symptomatic and/or ruptured, than true aneurysms (76% *vs.* 35%).[348]

In patients suspected of having an aneurysm of splanchnic arteries, is contrast-enhanced CT better than ultrasound techniques with or without contrast agent to establish the diagnosis?

Recommendations

- CT is recommended over ultrasound to diagnose and plan treatment of splanchnic artery aneurysms **(LoE 4, strong recommendation, strong consensus).**
- The CT protocol should be multiphasic and include non-contrast, arterial phase, and portal venous acquisition with thin reconstruction enabling adequate reconstruction **(LoE 4, strong recommendation, strong consensus).**

Ultrasound is a common imaging modality to diagnose and monitor abdominal aortic aneurysms, but is not the modality of choice in SAAs, as it is often limited by bowel gas or obesity. Moreover, the sensitivity of ultrasound to detect SAAs <3 cm is poor[349]. There is no head-to-head comparison between ultrasound and CT for diagnosing SAA, but in a review of the literature, a greater number of cases were diagnosed on CT than ultrasound[350]. Multiphasic contrast-enhanced CT including arterial phase is the best imaging modality.[350,351] CT allows for the diagnosis of SAA, as well as precise assessment of the location and size of the aneurysm. Moreover, CT helps guide treatment planning by showing the relationship of the SAA to the surrounding vasculature through multiplanar reformations and three-dimensional reconstructions. CT may also reveal complications, such as rupture or intra-abdominal haemorrhage. CT is also helpful in looking for the presence of other SAAs and associated underlying diseases.[348] MRI and magnetic resonance angiography can play a role in patients in whom CT is contraindicated. Yet, a study has reported that the sensitivity of magnetic resonance angiography was suboptimal for small aneurysms.[352]

In patients with aneurysm of splanchnic arteries, what work-up for risk factors should be performed to guide therapeutic strategy?

Recommendations

- Work-up for risk factors for splanchnic artery aneurysm development should search for: (i) signs of portal hypertension, which increases the risk of true aneurysms; (ii) arterial anomalies and aneurysms in other sites, as they suggest an arterial wall disease; and (iii) factors responsible for pseudoaneurysm including trauma, surgery, local infection or inflammation **(LoE 3, strong recommendation, strong consensus).**
- Work-up should assess the risk of rupture of these aneurysms to guide therapeutic strategy by: (i) analysing splanchnic artery aneurysm morphological characteristics, including size

and location, using contrast-enhanced CT; (ii) identifying patients with a higher risk of rupture, namely pregnant women and LT candidates; and (iii) searching for factors responsible for pseudoaneurysm (trauma, surgery, local infection or inflammation), since the risk of rupture of splanchnic artery aneurysms is higher in pseudoaneurysm than in true aneurysm **(LoE 3, strong recommendation, strong consensus).**

The type, the location, and the aetiology of SAA are key factors in guiding therapeutic strategy.

It is of utmost importance to distinguish true aneurysm from pseudoaneurysm, as the latter have a much higher risk of rupture (76.3% *vs*. 3.1% in the series of Pitton).[353] Recent surgery, trauma, and local infection or inflammation are the most common causes of pseudoaneurysm.[346] Therefore, they should be investigated in the comprehensive work-up. Another suggestive finding for pseudoaneurysms is the high frequency of symptoms (80% of pseudoaneurysms *vs*. 30% in true aneurysms).[347]

Work-up imaging is important for SAA management. It should be used to assess the location and size of SAAs, as well as to look for aneurysms in other sites. For instance, atherosclerotic SAAs are predominantly observed in the celiac axis and the splenic artery, and the presence of atherosclerotic arteries in other territories reinforces this likelihood. On the contrary, hepatic, gastroepiploic, and pancreaticoduodenal aneurysms are more often related to arterial dysplasia, local causes, or inflammation.[354] Presence of other aneurysms may favour the diagnosis of arterial or inherited diseases and could alter patient management. In a large retrospective study of SAAs, 3% of patients had concomitant visceral aneurysms and 14% of patients had concomitant non-visceral aneurysms, with the most common location being renal (7.4%) and abdominal aortic (3.7%).[355]

Lastly, specific work-up should be done according to SAA location and associated conditions. Celiac artery occlusive disease, mostly related to arcuate ligament syndrome, is a recognised cause of aneurysms affecting collateral vessels. In a review of the literature including 125 patients with celiac artery occlusive disease and SAAs, most aneurysms were located on pancreaticoduodenal arteries (105 patients), while the rest were on gastroduodenal arteries (10 patients), or both arteries (10 patients).[356]

SAAs are thought to have a particular tendency toward rupture, especially during the third trimester of pregnancy. Numerous case reports have been published, with pregnancy accounting for 20% to 50% of all ruptures.[357] SAAs also occur more commonly in LT candidates owing to cirrhosis-induced portal hypertension. In a recent systematic review including 159 patients with AAs, approximately one-third were treated prior to the LT. In 86 untreated asymptomatic patients, four cases of post-transplant rupture were observed.[358]

In patients with aneurysm of splanchnic arteries, is interventional treatment better than conservative treatment to reduce morbidity and mortality?

Recommendations

- Treatment decisions should be guided by the size, location and type of splanchnic artery aneurysms (true *vs.* pseudoaneurysm) (Fig. 5) **(LoE 3, strong recommendation, strong consensus).**
- In patients with small (below 2–2.5 cm in the largest axis), asymptomatic, true splanchnic artery aneurysms, conservative treatment is recommended. First follow-up contrast-enhanced CT should be performed 6 months to 1 year after initial diagnosis and subsequently every 3 years if size remains stable **(LoE 4, strong recommendation, strong consensus).**
- In patients with symptomatic or large (above 2–2.5 cm in the largest axis) or fast-growing true splanchnic artery aneurysms, and in all patients with splanchnic pseudoaneurysms (high risk of rupture), interventional treatment is recommended **(LoE 4, strong recommendation, strong consensus).**
- In patients with splenic aneurysm of any size, interventional treatment is recommended in women of child-bearing potential and in LT candidates, as the risk of rupture is high **(LoE 4, strong recommendation, strong consensus).**
- In patients with gastro and/or peripancreatic aneurysms related to celiac axis occlusion, interventional treatment is recommended **(LoE 4, strong recommendation, strong consensus).**
- In patients with splanchnic artery aneurysms and an indication for interventional treatment, endovascular treatment should be proposed over open surgery, as it is associated with similar mortality but reduced morbidity. Open surgery is indicated when the endovascular approach is not feasible **(LoE 3, strong recommendation, strong consensus).**

The level of evidence is low as there is no RCT. Yet, there are recent series with large numbers of patients, considering the rarity of the diseases, as well as a meta-analysis and systematic review [345,348,353]. There are no differences in long-term survival between patients who undergo interventional treatment and patients who are observed.[359] This lack of difference can be accounted for by the fact that small SAAs are monitored and large SAAs are subject to intervention. The treatment strategy for SAAs depends on the risk of rupture, as the mortality rate of ruptured SAAs is at least 10% and much higher in some conditions.[360] For instance, in the series of Tétreau *et al.* including 112 patients with SAAs, ruptured SAAs represented 30% of cases and were associated with a mortality rate of 9%.[348] Overall, in the literature, nearly one-fourth of visceral artery aneurysms presented with rupture.[346]

The natural course of asymptomatic, small-sized true SAAs has been analysed in several studies. In the series of Tétreau *et al.*, out of the 112 patients with SAAs, 23 asymptomatic patients with true aneurysms ≤2 cm (mostly hepatic or splenic) were managed conservatively and followed over a 2-year period. Growth was documented in only one patient, with a 22 mm true splenic aneurysm.[348] In the series of Corey *et al.*, out of the 264 SAAs in 250 patients, surveillance imaging was performed for 138 SAAs, including 124 SAAs <25 mm. In the latter, 10 of 124 (8%) grew in size over time and only two aneurysms reached the threshold of 25 mm. There was no rupture during the surveillance period.[359] In the series of Batagini *et al.*, out of 116 patients with SAAs, 74 patients with

87 SAAs were followed. The median growth for all aneurysms was 0.63 mm/year and only the splenic aneurysms presented significant growth of 1.08 mm per/year (±1.99), which was associated with the presence of portal hypertension.[361] The mean annual growth for splenic aneurysms <20 mm and >20 mm was not statistically significant (0.28 mm *vs.* 1.38 mm).[361] In the series of Erben *et al.*, out of the 122 patients, 101 patients with 108 SAAs were managed non-operatively. The mean follow-up was 50 months without any adverse events related to SAAs, including 10 patients with SAAs >2.0 cm. The mean observed growth rate for SAAs was 0.064 ± 0.18 cm/year.[362]

Based on this published literature, a reasonable cut-off for conservative treatment of true and asymptomatic SAAs is below 2-2.5 cm.[348,359,361,362]

Pseudoaneurysm

Most pseudoaneurysms are symptomatic and therefore intervention is warranted. Unlike true aneurysms, even small (<1 cm) pseudoaneurysms may rupture and therefore no effective cut-off diameter can be proposed to guide the treatment of asymptomatic patients. Thus, treatment should be considered for any pseudoaneurysm once diagnosed.[348,363,364]

Specific conditions

True gastroduodenal and pancreaticoduodenal aneurysms, in particular those associated with celiac artery occlusive disease, carry a risk of rupture that does not appear related to size and occurs even in aneurysms of <10 mm.[348,356,365,366] This is why intervention is indicated.[367,368]

Many case reports have described rupture of SAAs during pregnancy. Although rupture is rare, it is associated with a high mortality rate during pregnancy; 75% for the mother and 95% for the foetus.[369] This is why splenic aneurysms in women of child-bearing age should be treated. Yet, such an association was not reported in the largest recent studies [355]. SAAs occur more commonly in LT candidates owing to cirrhosis-induced portal hypertension and may rupture after LT. Therefore, treatment is indicated before LT.[358]

Endovascular treatment *vs.* surgery

No RCT has compared open *vs*. endovascular repair for the treatment of SAAs. Most studies, which have included patients treated either with an endovascular approach or surgery have not shown differences in mortality rate. One study reported a lower 30-day mortality rate after endovascular repair of ruptured SAAs compared with open repair of ruptured SAAs.[360] SAAs are more likely to be treated endovascularly with a shorter length of stay.[370]

In children with aneurysms of splanchnic arteries, should management be the same as in adults?

Recommendation

- Management should be the same in children as in adult patients **(LoE 4, strong recommendation, consensus).**

Visceral artery aneurysms are very rare in children and may be symptomatic or asymptomatic. There may be an over-representation in certain syndromes such as Wiskott-Aldrich syndrome,[371] Alagille syndrome,[372] or von Recklinghausen disease (neurofibromatosis type 1)[373] in which they may be life-threatening. Akin to what has been described in adults, children may also develop SAAs in the setting of portal hypertension, which can be life-threatening, especially in the peritransplant period.[374] In one study, 10% of children with portal hypertension were found to have SAAs on CT angiography, not visible by Doppler ultrasound. SAAs were present in children with splenomegaly, and in all but one patient the intrasplenic branches were affected. The median diameter of the SAAs was 6.5 mm (2.5-18 mm).[375] Given the high risk of mortality and the limited visibility on ultrasound, the use of CT angiography in children with long-standing portal hypertension is advisable, especially prior to LT.[374,375] Finally, visceral artery aneurysms should be considered part of the differential diagnosis of portal hypertension in infants, as reported in a 6-week-old presenting with an upper gastro-intestinal bleed.[376]

Akin to what has been described in adults, it is important to differentiate aneurysms and pseudoaneurysms. Pseudoaneurysms of the visceral arteries are associated with the same aetiologies and risks as those described in adults. Aetiologies include history of trauma or infections.[377] They were symptomatic in 10/11 cases in a retrospective study.[377] Nine patients underwent radiological embolisation and were asymptomatic at a follow-up of 1-24 months. Although children differ from adult patients in their ability to develop collaterals, it is still recommended to manage children using the same methods as in adults, owing to the risk of life-threatening bleeding.

Hepatic arterio-venous fistula

Hepatic arteriovenous fistulae (HAVF) are rare vascular communications occurring between a branch of the hepatic artery and portal vein branches or hepatic vein branches. In this section, HAVF is used broadly for any or all arterio-venous communications upstream of the hilum or in the liver, while the term arterio-portal fistula (APF) is specific to an artery draining into the portal circulation.

There are two main aetiologies of HAVF: congenital or acquired – the latter being either iatrogenic, accidental or associated with chronic liver disease or a tumour.[378,379] When congenital in origin, HAVF are referred to as arterio-venous malformations (AVMs).

Congenital forms are more often diffuse or multiple, while acquired fistulae are more commonly solitary. Although age at presentation differs between congenital and acquired, there are reports of HAVF thought to be AVMs presenting in adults spanning the ages of 30-75 years.[380] Modes of presentation include signs and symptoms of portal hypertension such as hematemesis or melena, ascites, splenomegaly, caput medusae or HE.[379] Diffuse or multiple HAVF should raise suspicion of hereditary haemorrhagic telangiectasia (HHT), for which the reader is referred to forthcoming guidelines.

APF may have one of three origins. The first is congenital. Under 50 cases have been reported in the literature with clinical presentation in children including diarrhoea, steatorrhoea, and failure to thrive in addition to the cardinal signs above.[381] Norton and co-authors suggested a classification according to

afferent blood supply: unilateral, bilateral, and complex.[382] The clinical relevance of understanding the anatomy may be that it could help predict *de novo* collateralisation after embolisation, which is more common in the complex forms, and which may ultimately require partial hepatectomy or LT.[382,383] Another aetiology of APF is chronic liver disease, in which changes in flow, such as the occlusion of small hepatic venules, may lead to intrahepatic vascular changes and ultimately APF.[384] The differential diagnosis in the cirrhotic liver includes HCC and haemangiomas.[385,386] In fact, it has been reported that 63% of HCC present with APF.[387,388] It follows that understanding the radiological characteristics of these lesions is essential to determine management. Knowing that most APF disappear, longitudinal follow-up is essential.[385,387,388] A low index of suspicion for these lesions is important as they may present with non-specific findings in a patient with liver disease such as abdominal pain and increased abdominal girth. Finally, there are many reports of APF arising after percutaneous liver biopsy, often in the setting of chronic liver disease or following abdominal trauma.[379,389–393] These may or may not be symptomatic and are amenable to the same management approaches as other forms.

Arteriovenous fistulae present similarly with abdominal distension, pain, gastro-intestinal bleeding and heart failure from high output states. The differential diagnosis of an HAVF communicating with a hepatic vein includes congenital forms, tumours (either primary or secondary, including angiomas), liver abscess and chronic liver disease,[394] and a history of trauma or liver biopsy.

In patients suspected of having hepatic arteriovenous fistula, is contrast-enhanced CT more accurate than ultrasound techniques to establish the diagnosis?

Statement

- Both Doppler ultrasound and contrast-enhanced CT are useful to establish diagnosis and may be complementary in equivocal situations **(LoE 4, strong recommendation, strong consensus).**

Recommendations

- Contrast-enhanced CT also provides information on the presence or not of extrahepatic arteriovenous fistula and should be used for treatment planning **(LoE 4, strong recommendation, strong consensus).**

Diagnosis and follow-up of HAVF is imaging-based both for arterioportal and arteriovenous forms. Ultrasound techniques with or without contrast are utilised, as is angio-CT. Each type of fistula has its own imaging characteristics, and understanding the differences is important as they guide management.

In patients with hepatic APF, early portal enhancement during the arterial phase of angio-CT is a characteristic finding together with reversed portal flow and early filling of the portal system on arterial phase.[395] Doppler ultrasound may also show a vascular mass in the liver or hepatomegaly. Both in children and adults, Doppler ultrasound is accepted to be very sensitive to detect HAVF, and the addition of contrast has not been shown to be of significant benefit in this indication.[396] Doppler ultrasound is rapid and reliable if the fistula is prehepatic, and angiography confirmatory.[382] Angio-CT may inform arteriography and embolisation decisions, especially in the presence of a tumour.

The imaging features of HAVF differ from APF in that rather than early filling of the portal tree during the arterial phase, there is early contrast in the hepatic vein(s) prior to the portal phase, at least focally at the sight of the fistula. As for hepatoportal fistulae, contrast-enhanced CT or Doppler ultrasound are the methods of choice for the diagnosis.

In patients with hepatic arteriovenous fistula, what work-up for risk factors should be performed to guide therapeutic strategy?

Recommendation

- Work-up for risk factors should include searching for: (i) a history of liver biopsy or surgery, liver interventional radiology, or liver trauma; (ii) features suggesting haemorrhagic telangiectasia, particularly in case of multiple fistulae; (iii) features suggesting liver malignancy; and (iv) features suggesting chronic liver disease in case of arterio-portal shunts **(LoE 4, strong recommendation, strong consensus).**

HAVF are most commonly related to trauma or malignancy and are typically solitary. In these instances, history and imaging will orient diagnosis,[397] although sometimes no clear risk factor is identified.

In adults, HCC is a very common cause of hepatic APF.[397–399] Therefore, primary liver tumours or metastases should be sought in case of an HAVF to orient management. Yet, many HAVF may resolve spontaneously, and may not warrant oncological treatment.[400,401] These are known as arterial pseudolesions. The challenge is to distinguish potentially malignant lesions from the benign pseudolesions. To this end, in one study which analysed 32 pseudolesions and 21 HCCs, it was suggested that the distinguishing features included shape, location, arterial liver perfusion, portal venous perfusion, and hepatic perfusion index. In this study, the combination of arterial liver perfusion and portal venous perfusion derived from perfusion CT was very accurate in discriminating between these two lesions.[384,402] Importantly, while pseudolesions can vary in aspect, HCCs are never wedge-shaped. Another study reported that hepatic APF were more common in haemangiomas than in HCC.[386]

Finally, in case of multiple intrahepatic APF or the association with extrahepatic AVMs or other clinical signs and symptoms suggestive of HHT, specialised advice should be sought and genetic work-up considered (https://hhtguidelines.org/liver/). For HHT, the reader is referred to specific guidelines.

In patients with hepatic arteriovenous fistula, is closure at the time of diagnosis recommended over a conservative approach to reduce morbidity and mortality?

Recommendations

- In patients with hepatic arteriovenous fistula without related symptoms, a conservative approach is recommended **(LoE 4, strong recommendation, strong consensus).**
- In patients with hepatic arteriovenous fistula with related symptoms, without HHT, closure at the time of diagnosis is recommended **(LoE 4, strong recommendation, strong consensus).**

It is often difficult to tease out whether symptoms are due to the fistula or to progressive liver disease, and therefore it is recommended that patients be referred to an expert centre. It is generally recommended that patients with severe symptoms, such as portal hypertension or gastrointestinal bleeding, receive prompt endovascular treatment using embolisation or coiling.[379] If the HAVF is the presenting sign of a liver tumour, management follows standard of care, and embolisation may be required.[403]

Among patients who are asymptomatic with an incidental finding of a single HAVF, a history of past liver biopsy is common. This subset of arteriovenous fistulae may resolve spontaneously.[378] Thus, in asymptomatic patients with no evidence of malignancy or other complication, longitudinal follow-up is acceptable, considering the differential criteria for pseudo-lesions and HCC described above. The optimal duration of conservative management is unclear.

In patients with isolated hepatic arteriovenous fistula, are endovascular approaches recommended over surgical ligation to reduce morbidity and mortality?

Recommendation

- In patients with isolated hepatic arteriovenous fistula requiring treatment, endovascular closure is the method of choice, while surgery may be an exceptional option for recurrent fistula despite repeated endovascular procedures **(LoE 4, strong recommendation, strong consensus).**

When required, the preferred treatment is endovascular embolisation. The usual approach is intra-arterial, but occasionally a venous approach may be preferable. Longitudinal follow-up is recommended using ultrasound to monitor for delayed opening of other hepatoportal fistulae. Surgical arterial ligation or partial hepatectomy are best reserved for patients in whom the fistula recurs after several rounds of embolisation.[404–406] Exceptionally, LT has been performed for this indication.[407] Finally, depending on anatomy, it is important to emphasise that the presence of both arterio-portal and arterio-venous fistulae raises the suspicion of HHT which should be investigated according to standard recommendations (https://hhtguidelines.org/).

In patients with diffuse or recurrent hepatic arteriovenous fistula, is adjuvant medical therapy recommended to reduce risk of recurrence?

Statement

- Outside the HHT setting, there is no evidence to support the use of adjuvant medical therapy to reduce risk of recurrence **(LoE 5, strong consensus).**

In venous and lymphatic malformations, the use of mTOR inhibitors is now standard of care because of the causal role of the target of rapamycin pathway in their aetiology and pathogenesis.[408–410] Response to sirolimus in arteriovenous malformations of the head and neck has been reported anecdotally.[411] There are no clinical reports of mTOR inhibitor use for HAVF. However, in an animal model of HHT, mTOR inhibition in combination with nintedanib blocked retinal arteriovenous fistulae and haemorrhage.[412] Whether this can be translated into clinical use for vascular malformations of the liver remains to be determined.

In children suspected of having hepatic arteriovenous fistula, should the approach be the same as in adults?

Recommendation

- The general approach to diagnosis and management in children should follow that in adults. However, there are two important differences to consider:
  - (i) rule out congenital haemangioma, which is managed medically **(LoE 3, strong recommendation, consensus)**;
  - (ii) use caution with volume of embolic agent in infants owing to the risk of migration **(LoE 5, strong recommendation, strong consensus).**

There is one clinical scenario where medical management is the mainstay of therapy –congenital haemangiomas – where systemic propranolol is the treatment of choice.[413,414] In the neonate, a haemangioma may present as a congenital intrahepatic AVM. Angio-CT is diagnostic.[415,416] Depending on haemodynamics and cardiovascular status, embolisation may be necessary in combination with propranolol.[417]

In the setting of embolisation for neurovascular indications, the migration of Onyx has been reported in small infants.[418]

Therefore, it follows that this is also something to consider in the case of HAVF.

Issues common to vascular liver diseases

In patients with vascular liver diseases, when should surveillance for gastro-oesophageal varices be performed to reduce morbidity and mortality?

Recommendations

- Surveillance for gastro-oesophageal varices is recommended when clinical, ultrasonographic, liver or spleen elastography data or platelet count suggest the presence of portal hypertension. Interpretation of these parameters can vary according to the type of vascular liver disease **(LoE 5, strong recommendation, strong consensus).**
- If no varices are observed at index endoscopy, the next endoscopy should be performed 2 years later. If small varices are observed at index endoscopy, the next endoscopy should be performed 1 year later (Fig. S3) **(LoE 5, strong recommendation, consensus).**

Development of portal hypertension, with the ensuing risk of gastro-oesophageal varices, is a hallmark in the evolution of vascular liver diseases. In general, in vascular liver disease, non-invasive markers are used to raise suspicion of the presence of portal hypertension and subsequently initiation of screening for gastroesophageal varices. The presence of portosystemic collaterals on imaging is the most sensitive sign of portal hypertension, which applies to patients with chronic PVT, PSVD or BCS.[419] The presence of splenomegaly and/or thrombocytopenia may suggest portal hypertension, but may also indicate an underlying haematological prothrombotic disorder. In recent PVT, screening for varices should be performed at diagnosis, and endoscopy repeated 1 year after PVT diagnosis in the absence of recanalisation.

Liver elastography is rarely useful, because, despite the presence of severe portal hypertension, LSMs can be normal or only slightly elevated in patients with chronic PVT or with PSVD.[101] By contrast, in patients with BCS increased liver stiffness may indicate increased liver congestion and portal hypertension.[420] Spleen stiffness measurement is a promising new method for the evaluation of portal hypertension.[421] In patients with PSVD, spleen stiffness measurement by transient elastography ≤40 kPa combined with bilirubin <1 mg/dl identifies patients with PSVD and portal hypertension with a probability of high risk varices <5%, in whom screening endoscopy can be spared.[422] Likewise, patients with portal cavernoma and spleen stiffness measurement by transient elastography ≤40 kPa have a very low probability of high-risk varices; around 40% of screening endoscopies could be spared using this approach.[423]

Given the favourable cost/benefit ratio of primary prophylaxis in patients with high-risk varices demonstrated in cirrhosis, and the assumption that similar benefits may apply to patients with vascular liver diseases, such as PSVD[97] or chronic PVT,[116] upper endoscopy is recommended to rule out oesophageal varices in uncertain cases.

In patients with vascular liver diseases, which treatment should be preferred for prophylaxis of portal hypertension-related bleeding to reduce morbidity and mortality?

Recommendations

- NSBBs or endoscopic treatment are recommended in primary prophylaxis for portal hypertension-related bleeding, and both in secondary prophylaxis, to reduce morbidity and mortality **(LoE 3, strong recommendation, strong consensus).**
- In patients with refractory portal hypertension-related bleeding, TIPS is recommended **(LoE 3, strong recommendation, strong consensus).**

Patients with vascular liver diseases are at risk of developing varices and variceal bleeding. However, in general, rebleeding rates and severity are lower than in patients with cirrhosis. In patients with cirrhosis, NSBBs modify the natural history of the disease and their effectiveness becomes more pronounced in the presence of hyperdynamic circulation, typically occurring with the development of clinically significant portal hypertension (*i.e.* HVPG ≥10 mmHg)[424] Conversely, the progressive development of hyperdynamic circulation is not universally observed in patients with vascular liver disease, as the pathophysiology of portal hypertension has been suggested to differ slightly from that of cirrhosis, especially in the early stages.[101,426,427] Despite these differences, NSBBs are recommended for patients with vascular liver diseases to prevent variceal bleeding. In the absence of data on the effect of NSBBs on preventing decompensation in patients with vascular liver disease, NSBBs are indicated only for patients with high-risk varices, in line with the Baveno VI guidelines for patients with cirrhosis.[428] While natural history studies and small clinical trials have shown the effectiveness of endoscopic therapy in preventing variceal bleeding, there is insufficient data to determine the preferred option between endoscopic therapy or NSBBs.[10,40,97,429,430]

Several concepts that have emerged in the field of cirrhosis over the past few years may not be directly applicable to patients with presinusoidal portal hypertension (typically PVT and PSVD) due to a lack of specifically generated data, and as such, their application cannot be recommended until proven. First, the definition of clinically significant portal hypertension, characterised by a HVPG ≥10 mmHg, as the target level associated with an increased risk of decompensation, does not hold true for PSVD and PVT. HVPG in these patients does not accurately reflect real portal hypertension, as it fails to capture its presinusoidal component. Endoscopic ultrasound-guided measurement of the portosystemic pressure gradient could overcome this limitation. However, this technique requires general anaesthesia, which probably makes estimation of the pressure gradient less reliable.[431] Consequently, patients with vascular liver diseases may experience

Table 11. Drugs associated with specific vascular liver disorders.

Drugs associated with specific vascular liver disorders	Drugs	Reference
Budd-Chiari syndrome, Portal vein thrombosis	Oral contraceptives, hormone replacement therapy	See 1.1
PSVD	Azathioprine, didanosine, stavudine, oxaliplatin, thioguanine, arsenic, trastuzumab emtansine	102
Peliosis	Anabolic steroids, oral contraceptives, thiopurines, tamoxifen	See 8.7 238,269–271
Non-obstructive sinusoidal dilation	Oral contraceptives, oxaliplatin-based chemotherapy, azathioprine	See 8.3 247,248,250,258–260
Sinusoidal obstruction syndrome	Actinomycin D, azathioprine, busulfan, carmustine, cytosine arabinoside, cyclophosphamide, dacarbazine, gemtuzumab ozogamicin, immune check-point inhibitors, melphalan, mercaptopurin, mitomycin, mycophenolate mofetil, oxaliplatin, pyrrozolidine alkaloids, urethane, tacrolimus, terbinafine, traditional herbal remedies, 6-mercaptopurine, 6-thioguanine	See box 1

decompensation at lower HVPG levels, challenging the applicability of the established threshold. Second, the potential benefit of treating patients with small or no varices remains elusive in PSVD and PVT. The exclusion of these patients from the PREDESCI trial hinders our ability to draw conclusions about the efficacy of interventions in this specific population. Third, unlike in cirrhosis, uncertainty persists regarding the superiority of carvedilol over traditional NSBBs (propranolol, nadolol) in PSVD and PVT. While carvedilol demonstrates a greater reduction in portal hypertension in cirrhosis, attributed to its dual action on portal blood flow and intrahepatic resistance, there is no rationale to expect a similar effect in patients with vascular liver diseases, in whom resistance primarily increases at the presinusoidal level.

In patients with portal hypertension-related bleeding refractory to medical therapy, TIPS is a good therapeutic option[128,228]. However, the criteria used to identify patients at high risk of rebleeding and mortality, where preemptive TIPS placement improves outcomes, have not been validated in individuals with PSVD or PVT without cirrhosis.

In patients with Budd-Chiari syndrome or PVT without cirrhosis, are direct oral anticoagulants recommended over vitamin K antagonists or low-molecular-weight heparin to reduce morbidity and mortality?

Recommendations

- In patients with recent PVT without cirrhosis, direct oral anticoagulants are suggested as an alternative to low-molecular-weight heparin and/or vitamin K antagonists, during the first 6 months after PVT diagnosis, to reduce morbidity and mortality **(LoE 3, weak recommendation, consensus).**
- In patients with chronic PVT without cirrhosis (*i.e.* >6 months after recent PVT diagnosis or portal cavernoma), direct oral anticoagulants may be preferred over vitamin K antagonists to facilitate adherence and improve safety **(LoE 2, weak recommendation, consensus).**
- In patients with Budd-Chiari syndrome, direct oral anticoagulants may be considered as an alternative to low-molecular-weight heparin and/or vitamin K antagonists to reduce morbidity and mortality, when liver function is preserved **(LoE 4, weak recommendation, consensus).**

DOACs offer simpler administration than LMWH and VKAs, a faster onset and offset of action, and a more predictable response than VKAs; they are currently the recommended first-line treatment for patients with lower limb deep vein thrombosis and pulmonary embolism. Evidence on their safety and efficacy in patients with PVT or BCS is growing, but no direct comparisons with LMWH and/or VKAs in RCTs involving patients without cirrhosis are available.

Data from observational studies in patients with PVT suggest good recanalisation rates and acceptably low bleeding rates with DOACs, and indirect comparisons with VKAs suggest similar safety and efficacy.[117] A single-arm, interventional study on rivaroxaban in the acute and long-term phase (*i.e.* the first 3 months) in patients with non-cirrhotic splanchnic vein thrombosis reported similar incidences of bleeding, recurrent thrombosis, and mortality compared with historical cohorts treated with LMWH and/or VKAs.[432] In a RCT on patients with chronic PVT, rivaroxaban 15 mg per day significantly reduced the incidence of recurrent venous thromboembolism without increasing major bleeding events compared with no anticoagulation.[123]

Information remains limited for patients with BCS and PVT associated with cancer.[38] In a recent retrospective observational study, 22 patients with BCS were effectively treated with DOACs, but the incidence rate of major bleeding was not negligible (8.8 per 100 patient-years). Conversely, the incidence rate of bleeding was low in a cohort of 51 patients with myeloproliferative neoplasm-associated splanchnic vein thrombosis treated with DOACs (0.8 per 100 patient-years).[433] Precautions regarding the use of DOACs are summarised in Table 12.

In patients with vascular liver diseases, which method of contraception is associated with a lower risk of thrombotic events?

Recommendation

- Intrauterine devices, mechanical contraception and microprogestatives are associated with a lower risk of thrombotic events and should be preferred over oestrogen-containing oral contraceptives **(LoE 3, strong recommendation, strong consensus).**

The use of oral contraceptives is a known risk factor for BCS, observed in about one-third of patients at diagnosis.[7] Indeed,

in a case-control study performed in the 80s, including 33 women with BCS and 128 case-matched controls, recent oral contraceptive use was associated with a HR for BCS of 2.37 (95% CI 1.05-5.34; p <0.02).[434] However, it should be noted that the oestrogen dose in contraceptive pills at that time was higher than nowadays. Moreover, outside of the vascular liver disease field, the risk of venous thromboembolism is known to be increased with oestrogen-derived oral contraceptives, but not with progestin-only contraceptives.[435] Finally, the temporal relationship between pregnancy and BCS reinforces the view that oestrogens favour BCS and that oestrogen-containing oral contraceptives are contraindicated in patients with BCS.

Although the association between exposure to oral contraceptives and PVT is less certain, hormonal contraception has been reported in about the half of female patients with recent PVT.[92] Furthermore, other risk factors for thrombosis are often present alongside oral contraceptive use in patients with splanchnic vein thrombosis.[436,437] For these reasons, oestrogen-derived oral contraceptives may be avoided in patients with PVT. Oestrogen-derived oral contraceptives may also be avoided in patients with PSVD without PVT, as PSVD is *per se* a risk factor for PVT.

Conversely, intrauterine devices and mechanical contraception do not increase the risk of thrombosis, and can therefore be prescribed in patients with BCS or PVT.

In patients with vascular liver diseases, which drugs should be avoided to minimise adverse events?

Recommendations

- Specific drugs known to be associated with vascular liver disorder development (Table 11) should be avoided or discontinued to avoid further progression of the disease **(LoE 4, strong recommendation, strong consensus).**
- Drugs associated with DILI (Table S2) may be used with caution to minimise adverse events, although there is no data to suggest a differential course of DILI in these patients. If used, regular monitoring of liver blood tests is suggested **(LoE 5, weak recommendation, consensus).**
- In patients with vascular liver diseases and impaired liver function and/or portosystemic shunting, certain drugs which have a high first-pass effect, depend on albumin binding or are metabolised by the liver (Table 12) may be used with caution or avoided **(LoE 5, weak recommendation, consensus).**

Table 12. Commonly prescribed drugs to use with caution in patients with impaired liver function (including cirrhosis), portosystemic shunts or specific types of vascular liver disorders.

Drugs to use with caution	Specific populations	Comment
Direct oral anti-coagulants	Child-Pugh B	Use with caution
	Child-Pugh C	Avoid[40]
	Renal insufficiency	Dose adjust; contraindicated if eGFR <30 ml/min for dabigatran and if eGFR <15 ml/min for apixaban, rivaroxaban and edoxaban
	Double or triple positive anti-phospholipid antibody syndrome	Avoid
Drugs with high rate of first-pass extraction (*i.e.* beta adrenergic blockers, calcium channel antagonists, cisapride and other prokinetic agents, antipyschotics, anti-anxiety and sedative agents, anti-parkinson drugs, antidepressants, sumatriptan, fluvastatin, lovastatin, morphine	TIPS or portosystemic shunting	Dose reduction needed[438]
Midazolam, nifedipine, isradipine, QTc prolonging medications (fluoroquinolones), sedatives (amitriptyline, diazepam, zolpidem)	TIPS or portosystemic shunting	Dose reduction needed, QTc monitoring needed[438]
Carvedilol, propranolol	Child-Pugh B and C	Use with caution, dose adjustment may be needed in higher Child-Pugh class[438,457]
Simvastatin	Child-Pugh B and C	Avoid in high doses (*i.e.* 40 mg) in Child-Pugh B or C Safe in lower doses (*e.g.* 20 mg)[438,458]
Atorvastatin	Child-Pugh B and C	Avoid in Child-Pugh B or C[438,459]
Acetaminophen	Child-Pugh B and C	Maximum of 2-3 g/day[438,460]
Non-steroidal anti-inflammatory drugs (NSAIDS), angiotensin-converting-enyzme inhibitors, angiotensin II antagonists, or a1-adrenergic receptor blockers	Ascites	Avoid due to increased risk of renal impairment[438,461]
Pantoprazole, lansoprazole, cimetidine	Chronic liver diseases	Restrict to well established indications[438,459]
Barnidipine, isradipine, nicardipine, nitrendipine	Cirrhosis	Avoid[438,459]
Budesonide	Portal hypertension	Avoid (high first-pass effect)[459]
Proton-pump inhibitors, antibiotics (piperacillin/tazobactam, meropenem, ciprofloxacin, norfloxacin, metronidazole), antifungals (fluconazole), sedatives (opioids, benzodiazepines)	Patients at risk of hepatic encephalopathy	Associated with acute hepatic encephalopathy[462]
Triamterene	Cirrhosis	Avoid[438,459]

As stated before in this guideline, several drugs are known to be associated with the development of vascular liver disorders (Table 11). Although there is little data, it is reasonable to assume that removal of this predisposing factor would avoid further progression. Furthermore, many drugs are associated with drug-induced liver injury (DILI) in patients with *a priori* healthy livers (Table S2). One would assume that patients with non-healthy livers, especially those with chronic liver disease, would be more prone to DILI due to a number of factors which interfere with drug handling: reduced hepatic blood flow, portosystemic shunting, hypoalbuminemia, increased volume of distribution, reduced first-pass metabolic clearance, reduced glutathione storage, and impaired biliary and renal elimination.[438] However, there is very little data to support this assumption, in particular for drugs causing idiosyncratic liver injury.[439] Nevertheless, it is generally accepted that the consequences of such a DILI would probably be more severe in the context of preexisting liver disease and impaired liver function.[438] In patients with vascular liver disorders, there is no data to suggest a differential course of DILI. Therefore, these drugs are to be used with caution, and regular monitoring of liver tests may be needed. Finally, several commonly prescribed drugs have a high first-pass effect, depend on albumin binding, or are metabolised by the liver (Table 12). These drugs are either contraindicated or should be used with dose adjustment in patients with vascular liver disorders, cirrhosis, and/or portosystemic shunting, including TIPS.

In patients with vascular liver diseases, how should pregnancy be managed to reduce maternal and foetal morbidity and mortality?

Recommendations

Before conception:

- In patients with vascular liver diseases of childbearing age, advice on pregnancy should be offered early after liver disease diagnosis. Pregnancy should be planned when the liver disease and the prothrombotic condition are well-controlled **(LoE 3, strong recommendation, strong consensus).**
- In patients with vascular liver diseases and myeloproliferative neoplasm, cytoreductive therapy should be stopped before conception as it is teratogenic **(LoE 3, strong recommendation, consensus).**

Anticoagulation:

- Vitamin K antagonists or direct oral anticoagulants should be switched to low-molecular-weight heparin as soon as pregnancy is confirmed and at least before the 4th week of gestation. In this setting, low-molecular-weight heparin should then be continued during the whole pregnancy **(LoE 3, strong recommendation, consensus).**
- In patients with vascular liver diseases not receiving anticoagulants, prophylaxis of thromboembolic events using low-molecular-weight heparin may be considered for 6 weeks after delivery to prevent thrombotic events **(LoE 5, weak recommendation, consensus).**

Portal hypertension:

- In patients with vascular liver diseases, gastroesophageal varices should ideally be searched for in the year before conception, or during the second trimester of pregnancy if not done before conception **(LoE 4, strong recommendation, strong consensus).**
- In patients with vascular liver diseases, variceal haemorrhage occurring during pregnancy should be prevented and managed as in non-pregnant patients **(LoE 4, strong recommendation, consensus).**

Delivery:

- Vaginal delivery should be preferred over caesarean section, even in cases of portal hypertension. Caesarean section should be reserved for obstetrical indications **(LoE 4, strong recommendation, consensus).**
- Platelet count >20x10^9/L and >50x10^9/L should be considered as safe for vaginal delivery and caesarean section, respectively. Platelet count >75x10^9/L should be considered safe for epidural anaesthesia and >50x10^9/L for spinal anaesthesia **(LoE 5, strong recommendation, consensus).**

Post-partum:

- Oestrogen-derived oral contraceptives should not be administered post-partum **(LoE 5, strong recommendation, consensus).**
- Treatment with beta-blockers and warfarin is possible during breastfeeding, while other vitamin K antagonists or direct oral anticoagulants are contraindicated **(LoE 4, strong recommendation, consensus).**

Pregnancy is not contraindicated in women with BCS and controlled disease. Indeed, five retrospective studies, including 97 pregnancies occurring in 59 patients between 1985 and 2021, reported no maternal death.[440–444] Nearly 50% of the women had a TIPS, angioplasty or surgical portosystemic shunts prior to conception, and all had compensated disease at the time of conception. Liver complications during pregnancy were rare in women with known and treated BCS before pregnancy: 5 pregnancies were complicated by ascites or pulmonary hypertension. Bleeding events occurred in women receiving anticoagulation and were unrelated to portal hypertension. Intrahepatic cholestasis of pregnancy and hypertensive disorders of pregnancy were the most common pregnancy-related diseases. The reported rate of miscarriage or ectopic pregnancy before 20 weeks' gestation was about 30%, higher than in healthy women of similar age. On the other hand, after 20 weeks' gestation, about 90% of the babies were healthy, but the rate of prematurity was high. There was no congenital malformation.

The outcome of pregnancy in women with PVT is good when the disease is treated and well-controlled.[445,446] Five

studies assessed the outcome of pregnancy in a total of 260 women with known and controlled PVT.[443,445,447–449] There was no maternal death, and the rate of live births was high (about 85%, comparable to that in the general population). However, the rates of prematurity (11%) and foetal death (2%) appeared to be higher than in the general population. Concerning maternal outcome, no splanchnic vein rethrombosis was observed, but the rate of preeclampsia was high (4%), likely explained by thrombotic occlusion of the placental circulation, especially in women with underlying prothrombotic disorders. Bleeding related to portal hypertension was a rare complication during pregnancy when adequate prophylaxis had been applied (3% haemorrhages, 50% without adequate prophylaxis). Overall, pregnancy should not be contraindicated if the PVT and underlying thrombotic factors are controlled.

Data on pregnancy in patients with PSVD are mainly derived from a VALDIG study gathering 24 pregnancies in 16 women with known PSVD.[450] At conception, two out of the 16 women had detectable ascites and others were asymptomatic. Out of these 24 pregnancies, there were four miscarriages, one ectopic pregnancy, and one medical termination of pregnancy at 20 weeks of gestation. Out of the 18 other pregnancies reaching 20 weeks of gestation, there were nine preterm and nine term deliveries. All infants were healthy at delivery, but one died at day 1 of unknown cause and one at day 22 of infectious meningitis; both were preterm. Concerning mothers, two had worsening of ascites, two had variceal bleeding despite NSBB use during pregnancy, and one developed a thrombosis in the main portal vein early postpartum. Genital bleeding occurred in three patients, including two receiving anticoagulation. All 16 women were alive and asymptomatic after a median follow-up of 27 (9-93) months after last delivery. Altogether, the overall outcome of women with PSVD who become pregnant is favourable despite a significant incidence of complications related to portal hypertension, and pregnancy should not be contraindicated in patients with PSVD. Foetal outcomes are favourable in most pregnancies reaching 20 weeks of gestation.

In all patients with vascular liver disease, pregnancy should be planned, and a preconception visit is needed to i) inform the patient about expected outcomes, ii) ensure portal hypertension and underlying prothrombotic factors are controlled before conception, and iii) adjust drug prescriptions.[446] All VKAs must be switched to LMWH before the 4th week of gestation, as VKAs cross the placenta and can cause foetal haemorrhage and foetal VKA syndrome, especially between 6 to 12 weeks of gestation.[451]

Details on practical management of women with vascular liver diseases considering pregnancy, or pregnant, can be found elsewhere.[446,452]

In patients with vascular liver diseases, which psychological and social measures should be added to conventional management to reduce morbidity and improve quality of life?

Recommendation

- Systematically assessing the psychological and social impact of the disease is recommended to identify issues and refer patients to dedicated professionals and patient associations **(LoE 5, strong recommendation, strong consensus).** Specific tools to measure the impact of the disease on quality of life are lacking.

Patients with vascular liver diseases often face diagnostic delays, uncertainty, fear of complications, multiple hospital visits, and interventions that adversely impact their health-related quality of life. Many individuals with vascular liver diseases are economically active, and as with many rare diseases, there are health and social inequalities. Additionally, female patients with vascular liver diseases are often young women who may experience fear related to infertility or adverse pregnancy outcomes, further negatively affecting their quality of life. Patient-reported outcomes (PROs) can serve as valuable clinical markers for a comprehensive assessment of treatment effectiveness.[453] PROs are increasingly recognised as a direct measure of success for high-quality, patient-centred care. These outcomes encompass patient-generated data, including assessments of well-being, symptoms, physical and emotional function, and distress, all in a standardised format.[454] PROs relevant to patients with vascular liver disease have not been identified so far.

Patients' perceptions of their treatment have been demonstrated to influence their quality of life in specialised care and the dynamics of the patient-doctor relationship in the context of prolonged therapies, such as anticoagulation.[455] Patient satisfaction with medical care has been shown to correlate with a better quality of life and *vice versa*.

Partnering with patient associations is essential as it may contribute to reducing morbidity and improving patients' quality of life. Patient associations provide essential support through community building, advocacy for better healthcare policies, educational resources, and access to psychosocial support. By fostering a sense of belonging, raising awareness, and actively participating in research efforts, patient associations play a crucial role in enhancing early diagnosis, treatment options, and overall well-being for individuals with rare diseases including PSVD.

In patients with vascular liver diseases, what expertise is required for initial management and follow-up?

Recommendation

- Initial and follow-up management requires a multidisciplinary team including at least hepatologists, pathologists, radiologists, interventional radiologists, haematologists and/or vascular physicians, and liver surgeons. The centre should have expertise in TIPS placement, portal vein recanalisation, LT and in critical care management of patients with liver disease **(LoE 5, strong recommendation, strong consensus).**

As noted throughout the CPG, vascular liver diseases are rare disorders that may require a comprehensive and sometimes difficult diagnostic and therapeutic process, necessitating involvement of a multidisciplinary team. The presence of frequent, sometimes severe, comorbidities, the frequent use of anticoagulation, the need to perform TIPS in the setting of possible hepatic or portal vein thrombosis and/or surgery in the setting of severe portal hypertension and multiple abdominal collaterals make the management of these patients challenging. This is particularly important as the rarity of these disorders means that professionals from non-referral centres encounter very few such patients, making adequate training difficult. Therefore, these patients must be managed by a multidisciplinary team in expert referral centres for rare vascular liver diseases.

Appendix. Delphi round agreement on the recommendations of the present clinical practice guidelines.

Recommendation/statement	Consensus
The presence of local risk factors including solid abdominal cancer and intrabdominal inflammation or infections should be carefully investigated. In the absence of solid cancer, patients should be extensively assessed for the presence of underlying systemic risk factors (Table 3) **(LoE 2, strong recommendation).**	93%
Therapeutic strategies, particularly the selection of different anticoagulant agents, should be based on the underlying risk factors for thrombosis (Table 3). The duration of anticoagulant treatment should consider whether these risk factors are transient or permanent in nature **(LoE 2, strong recommendation).**	100%
The same work-up should be performed in children as in adults, bearing in mind that age-specific cut-offs should be considered for inherited thrombophilia (protein C, protein S, and antithrombin levels). If clinical suspicion persists, testing should be repeated in adolescence **(LoE 4, strong recommendation).**	100%
In patients with acute or chronic liver disease, Budd-Chiari syndrome should be systematically sought **(LoE 2, strong recommendation).**	97%
Doppler ultrasound should be used as the first-line examination to diagnose Budd-Chiari syndrome **(LoE 2, strong recommendation).**	100%
Contrast-enhanced cross-sectional imaging by CT or MRI is recommended as the next step to confirm the diagnosis and evaluate the feasibility of treatment options **(LoE 2, strong recommendation).**	97%
In patients suspected of having Budd-Chiari syndrome with patent hepatic veins on imaging, a liver biopsy is recommended to diagnose small hepatic vein Budd-Chiari syndrome **(LoE 3, strong recommendation).**	97%
In patients with radiologically confirmed Budd-Chiari syndrome, a liver biopsy is not recommended **(LoE 2, strong recommendation).**	93%
In patients with primary, non-fulminant, Budd-Chiari syndrome, a stepwise management strategy should be followed consisting of anticoagulation and treatment of underlying conditions, followed consecutively by percutaneous angioplasty, TIPS, and LT in non-responsive patients **(LoE 2, strong recommendation).**	100%
Patients with Budd-Chiari syndrome should therefore be treated in collaboration with centres with expertise in vascular liver diseases and LT **(LoE 5, strong recommendation).**	100%
Therapeutic anticoagulation should be initiated as soon as possible after diagnosis and continued indefinitely, unless contraindicated **(LoE 2, strong recommendation).**	100%
Low-molecular-weight heparin followed by vitamin K antagonists is the recommended anticoagulation therapy **(LoE 3, strong recommendation).**	100%
Unfractionated heparin should be avoided due to the risk of heparin-induced thrombocytopenia **(LoE 3, strong recommendation).**	100%
Direct oral anticoagulants may be considered in patients with preserved liver function **(LoE 4, weak recommendation).**	100%
Proper variceal prophylaxis should be ensured to avoid bleeding, but it should not delay initiation of anticoagulation **(LoE 3, strong recommendation).**	97%
In patients with short-segment stenoses in the inferior vena cava or hepatic veins, percutaneous transluminal balloon angioplasty should be considered **(LoE 3, strong recommendation).**	100%
In cases where medical management alone is insufficient to alleviate symptoms and percutaneous transluminal balloon angioplasty is not an option or has failed, TIPS is the recommended next step **(LoE 3, strong recommendation).**	100%
In patients with acute liver failure, emergency TIPS should be attempted, while in parallel listing the patient for LT, although transplantation may not always be needed **(LoE 3, strong recommendation).**	100%
In patients with liver disease not responding to medical or interventional therapy or in those with HCC, LT should be considered **(LoE 3, strong recommendation).**	100%
The currently available prognostic scores should not determine individual patient management alone but can be used for research purposes **(LoE 3, strong recommendation).**	100%
In patients with chronic Budd-Chiari syndrome, surveillance for HCC should include imaging and AFP measurement every 6 months (Fig. 1) **(LoE 3, strong recommendation).**	97%
An AFP level of >15 ng/ml should raise suspicion for HCC **(LoE 3, strong recommendation).**	100%
MRI, preferably with hepatobiliary contrast agents, is recommended to differentiate between benign (hyperintense on T1, hypo/isointense on T2, hyperintense on hepatobiliary contrast sequences) and malignant (hypointense on T1, hyperintense on T2, hypointense on hepatobiliary contrast sequences) lesions **(LoE 3, strong recommendation).**	100%
For lesions suspected of being HCC, histological confirmation should be obtained **(LoE 3, strong recommendation).**	93%
There is currently no solid evidence to recommend a treatment strategy different from that proposed for patients with other chronic liver diseases. All available treatment options for HCC, including LT, should be considered on a case-by-case basis **(LoE 4, strong recommendation).**	100%
Endovascular management is suggested as the first-line therapy in children, combined with post-procedure anticoagulation to prevent recurrence. LT can be considered when endovascular management is not possible or fails **(LoE 5, weak recommendation).**	93%
In patients with or without cirrhosis with PVT, a standardised description of initial site, extent, percent occlusion of main portal vein lumen, and time course (Table 4) is required to assess evolution **(LoE 5, strong recommendation).**	97%

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Appendix. (*continued*)

Recommendation/statement	Consensus
A complete clinical evaluation should be performed including searching for risk factors for cirrhosis and conditions associated with PSVD (Table 5), liver blood tests, evaluation of liver morphology using imaging, and LSM **(LoE 5, strong recommendation).**	97%
A liver biopsy should be considered to rule out cirrhosis or PSVD in the presence of at least one of the following features: a condition strongly associated with the presence of cirrhosis or PSVD, persistent liver blood test abnormalities, abnormal liver morphology on imaging, or elevated LSM **(LoE 5, strong recommendation).**	100%
In patients with recent or chronic PVT/portal cavernoma without known cirrhosis, a liver biopsy has an impact on patient management: (i) when it shows cirrhosis, because screening for liver cancer is indicated; and (ii) when it shows PSVD or cirrhosis in the setting of portal vein recanalisation because both may favour placing a TIPS at the same time as recanalising the portal vein **(LoE 3).**	93%
In patients with chronic PVT/portal cavernoma without known cirrhosis, a liver biopsy should be performed: (i) to rule out underlying liver disease when there are unexplained persistently abnormal liver blood tests, liver morphology suggestive of cirrhosis, or elevated LSM; and (ii) prior to portal vein recanalisation **(LoE 5, strong recommendation).**	96%
Ultrasound with or without contrast agent is as good as contrast-enhanced CT or contrast-enhanced MRI to diagnose recent PVT **(LoE 5, strong recommendation).**	79%
Contrast-enhanced CT or contrast-enhanced MRI should be used to characterise the extension of PVT (vessels affected and degree of occlusion of the lumen) as they perform better than ultrasound with or without contrast agent **(LoE 5, strong recommendation).**	100%
Contrast-enhanced CT should be used to characterise possible signs of intestinal ischaemia, as it performs better than other imaging techniques **(LoE 5, strong recommendation).**	100%
Anticoagulation should be initiated as soon as possible, since early initiation of anticoagulation may reduce the risk of developing intestinal ischaemia and increases the probability of portal vein recanalisation **(LoE 4, strong recommendation).**	100%
Anticoagulation should be continued for at least 6 months (see "In which patients with chronic PVT/portal cavernoma without cirrhosis, is anticoagulation recommended to prevent thrombotic events?") **(LoE 4, strong recommendation).**	100%
Anticoagulation, initiated as soon as possible, is the treatment of choice. If there are signs of intestinal ischaemia and no early improvement with anticoagulation, thrombolysis and/or endovascular interventions should be considered in expert centres, while being evaluated by surgeons for potential surgical resection (**LoE 5, strong recommendation).**	100%
The same management strategies used in adults may be applied in children except in the neonatal setting and in premature babies **(LoE 4, weak recommendation).**	96%
In patients with chronic PVT/portal cavernoma without cirrhosis and with a major and permanent prothrombotic risk factor (Table 3), long-term anticoagulation is recommended to prevent thrombosis recurrence (Fig. 2) **(LoE 1, strong recommendation).**	100%
In the remaining patients, thrombosis recurrence is less common, but anticoagulation can be considered to prevent thrombosis recurrence. Extension of thrombosis and factor VIII or D-dimer levels may help guide the decision **(LoE 2, weak recommendation).**	93%
Patients with chronic PVT/portal cavernoma without cirrhosis, and refractory complications of portal hypertension (recurrent or refractory gastrointestinal bleeding related to portal hypertension, refractory ascites) or portal cavernoma cholangiopathy, should be referred to expert centres for endovascular portal vein recanalisation with or without TIPS (Fig. S1); assessment of feasibility should consider intrahepatic portal branches patency and the extent of portal cavernoma **(LoE 3, strong recommendation).**	100%
In patients with chronic PVT/portal cavernoma without cirrhosis, without refractory complications of portal hypertension or portal cavernoma cholangiopathy, preventive portal vein recanalisation with or without TIPS is not generally recommended (Fig. S1) **(LoE 4, strong recommendation).**	97%
In patients with chronic PVT/portal cavernoma without cirrhosis with symptomatic portal cavernoma cholangiopathy (cholangitis, pancreatitis, jaundice, or pruritus), ursodeoxycholic acid and/or endoscopic or radiological biliary stenting, and/or portal vein recanalisation are recommended to prevent or treat biliary complications (Fig. S2) **(LoE 4, strong recommendation).**	100%
In patients with chronic PVT/portal cavernoma without cirrhosis and with asymptomatic portal cavernoma cholangiopathy, endoscopic or radiological biliary stenting, and portal vein recanalisation are not generally recommended (Fig. S2) **(LoE 4, weak recommendation).**	100%
Restoration of portal blood flow through Meso-Rex bypass or portal vein recanalisation is recommended in children regardless of the presence of symptoms **(LoE 4, strong recommendation).**	97%
When Meso-Rex bypass or portal vein recanalisation are not feasible, watchful management of the complications of portal hypertension is recommended **(LoE 4, strong recommendation).**	97%
In patients with complications of portal hypertension, porto-caval surgical shunt (spleno-renal or mesenteric to caval shunting) may be considered to delay or avoid LT **(LoE 4, weak recommendation).**	100%
MASLD may be associated with an increased risk of PVT development. Eradication of HCV does not influence the development of PVT. Data on other causes of cirrhosis are lacking **(LoE 3).**	93%
Screening for PVT should be continued regardless of treatment for the aetiology of cirrhosis **(LoE 4, strong recommendation).**	100%
In patients with cirrhosis who are potential LT candidates, surveillance for PVT (*e.g.* every 6 months) is recommended to improve feasibility and outcomes of LT **(LoE 2, strong recommendation).**	100%
In patients with cirrhosis who are not potential LT candidates, surveillance for PVT (*e.g.* every 6 months) is suggested, particularly in those without contraindications to anticoagulation, since anticoagulation has been shown to improve outcomes **(LoE 3, weak recommendation).**	100%
In patients with Child-Pugh B and C cirrhosis without PVT, anticoagulation may reduce morbidity and mortality **(LoE 2).**	96%
Work-up for risk factors for thrombosis is not recommended to guide management **(LoE 2, strong recommendation).**	96%

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Appendix. (*continued*)

Recommendation/statement	Consensus
In patients with cirrhosis and PVT who are potential LT candidates, anticoagulation should be used regardless of degree of occlusion or extension of PVT, to improve feasibility and outcomes of LT **(LoE 3, strong recommendation).**	100%
In patients with cirrhosis who are not potential LT candidates, anticoagulation may be used for PVT with total occlusion or >50% occlusion of the main portal vein, with or without superior mesenteric vein extension, to improve outcomes **(LoE 3, weak recommendation).**	97%
In patients with cirrhosis who are not potential LT candidates, anticoagulation may be considered for PVT with <50% occlusion of the main portal vein, which progresses over 3-6 months or extends to the superior mesenteric veins, to improve outcomes **(LoE 3, weak recommendation).**	100%
In patients with cirrhosis who are not potential LT candidates, and who have PVT with <50% occlusion of the main portal vein, surveillance is recommended and anticoagulation can be considered to improve outcomes **(LoE 4, weak recommendation).**	100%
Direct oral anticoagulants can be used in patients with PVT and Child-Pugh A or B cirrhosis; however, owing to insufficient evidence, they cannot be recommended over vitamin K antagonists or low-molecular-weight heparin to reduce morbidity and mortality. In patients with Child-Pugh C cirrhosis, direct oral anticoagulants are not recommended **(LoE 3, weak recommendation).**	100%
In patients with cirrhosis and PVT who have complications of portal hypertension, such as variceal bleeding or recurrent ascites, TIPS may be considered over anticoagulation alone to reduce morbidity **(LoE 2, weak recommendation).**	100%
In patients with cirrhosis and PVT which progresses despite anticoagulation, TIPS may be considered over anticoagulation alone to reduce morbidity **(LoE 2, weak recommendation).**	97%
Routine anticoagulation is not recommended to improve recanalisation rates after TIPS **(LoE 2, strong recommendation).**	100%
In patients with cirrhosis and Yerdel grade 1 or 2 PVT (Table S1) at the time of LT, anticoagulation after transplantation is not suggested to prevent recurrence of PVT **(LoE 4, weak recommendation).**	96%
In patients with cirrhosis and Yerdel grade 3 or 4 PVT (Table S1) at the time of LT, no recommendation can be made in favour or against anticoagulation after transplantation to prevent recurrence of PVT **(LoE 4, weak recommendation).**	93%
In patients with signs of portal hypertension, LSM <10 kPa, HVPG <10 mmHg, and smooth liver surface together with a normal-size or enlarged segment IV, especially in the presence of associated disorders or drugs listed in Table 5, should raise suspicion of PSVD **(LoE 3, strong recommendation).**	100%
In patients without signs of portal hypertension, unexplained liver blood test abnormalities should raise suspicion of PSVD, particularly in the presence of associated disorders or exposure to drugs listed in Table 5 **(LoE 3, strong recommendation).**	100%
A liver biopsy should be performed to make a diagnosis of PSVD (Table 7) **(LoE 3, strong recommendation).**	100%
An extensive work-up for HIV infection, thrombophilia, haematological disorders, immune/inflammatory/systemic diseases, as well as exposure to drugs, is recommended to identify conditions associated with PSVD (Table 5) **(LoE 3, strong recommendation).**	100%
Routine genetic testing for familial forms of PSVD cannot be recommended systematically **(LoE 4, weak recommendation).**	97%
Initial work-up should also include laboratory investigations and contrast-enhanced imaging, preferably CT, to search for other causes of liver disease and evaluate patency of the splanchnic venous system **(LoE 3, strong recommendation).**	97%
Conditions associated with PSVD have prognostic value. It is not known whether treating associated conditions has an impact on PSVD outcome **(LoE 3).**	100%
Surveillance for PVT every 6 months is recommended **(LoE 4, strong recommendation).**	97%
Surveillance for HCC cannot be recommended **(LoE 4, strong recommendation).**	100%
No recommendation can be made regarding anticoagulation therapy to prevent the development of PVT due to the absence of data **(LoE 4).**	100%
In patients with PSVD and severe or refractory portal hypertension-related complications, TIPS and/or LT are recommended to improve long-term outcomes **(LoE 3, strong recommendation).**	100%
Pre-LT evaluation should include careful evaluation of associated conditions that may impact outcome **(LoE 3, strong recommendation).**	100%
Diagnosis and management in children may follow the recommendations proposed for adults **(LoE 4, weak recommendation).**	96%
Sinusoidal dilatation is suspected when CT and/or MRI show a “mosaic enhancement pattern” on late hepatic arterial phase or portal venous phase, that fades on delayed phase. Non-obstructive sinusoidal dilatation should be suspected in the absence of any cause of hepatic venous outflow obstruction, including Budd-Chiari syndrome, right heart failure or chronic pericarditis **(LoE 4, strong recommendation).**	100%
In patients suspected of having non-obstructive sinusoidal dilatation based on imaging findings, liver biopsy is not systematically recommended to establish the diagnosis **(LoE 4, weak recommendation).**	96%
Liver biopsy can be considered when imaging findings persist 6 months after removing potential aetiological factors and/or are diffuse **(LoE 4, weak recommendation).**	93%
Work-up aimed at detecting associated conditions should include, depending on the clinical context **(LoE 4, strong recommendation, strong consensus):** ◦ History of drug use (including oral contraceptive use) ◦ Screening for solid tumours ◦ Screening for bacterial infections (*e.g.* pyelonephritis) ◦ Screening for myeloid or lymphoproliferative disorders, including Castleman disease ◦ Testing for HIV infection ◦ Screening for antiphospholipid antibody syndrome ◦ Screening for inflammatory bowel disease and for connective tissue disorders	97%
There is currently no data on the long-term outcomes of patients with non-obstructive sinusoidal dilatation **(LoE 5).**	100%
Follow-up including liver blood tests and imaging may be proposed. First follow-up may be 6 months to 1 year after initial diagnosis, with subsequent follow-up visits at longer intervals, if liver status remains stable **(LoE 5, weak recommendation).**	100%

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Appendix. (*continued*)

Recommendation/statement	Consensus
In patients with non-obstructive sinusoidal dilatation receiving platinum-based chemotherapy, discontinuation of this therapy is not recommended **(LoE 3, strong recommendation).**	100%
In patients with non-obstructive sinusoidal dilatation receiving oral contraceptives, discontinuation of this therapy may be considered to reverse sinusoidal dilatation **(LoE 4, strong recommendation).**	100%
There are no specific imaging features for peliosis hepatis **(LoE 4).**	100%
Peliosis hepatis should be suspected in the case of focal lesions mimicking tumours, particularly in the case of strong hyperintensity on T2 and persistent enhancement on CT/MRI during delayed phase. Diagnosis of peliosis hepatis requires a liver biopsy showing blood-filled spaces not entirely lined with endothelial cells. Reticulin fibres may be absent **(LoE 4, strong recommendation).**	100%
Predisposing conditions should be removed when feasible **(LoE 4, strong recommendation).**	100%
MRI is suggested to monitor disease progression. First follow-up may be 6 months to 1 year after initial diagnosis, with subsequent follow-up visits at longer intervals, if liver status remains stable **(LoE 5, weak recommendation).**	100%
In patients with peliosis hepatis and suspicion of complications, CT or MRI is suggested to diagnose haemorrhage. Management of haemorrhage should be discussed with expert centres considering simple surveillance, interventional radiology and surgery **(LoE 5, weak recommendation).**	100%
Management in children should follow the adult recommendations **(LoE 4, strong recommendation).**	96%
Prophylaxis with ursodeoxycholic acid is recommended in all patients to decrease the incidence of sinusoidal obstruction syndrome **(LoE 1, strong recommendation).**	100%
Defibrotide prophylaxis is generally not recommended to prevent sinusoidal obstructive syndrome **(LoE 2, strong recommendation).**	100%
The following signs should raise suspicion of sinusoidal obstruction syndrome: (i) clinical manifestations including hepatomegaly, hepatalgia, fluid retention with ascites, weight gain, transfusion refractory thrombocytopenia, jaundice; (ii) elevated LSM; (iii) ultrasound findings including hepatomegaly, gallbladder wall thickening, signs of portal hypertension (splenomegaly, ascites, decrease in velocity or reversal of the portal venous flow); and (iv) contrast-enhanced CT or MRI findings showing mosaic enhancement pattern on late arterial phase or on portal venous phase. Signs typically occur within 21 days after HSCT, but late-onset sinusoidal obstruction syndrome is possible after this time interval **(LoE 3, strong recommendation).**	100%
Criteria adjusted from EBMT 2023 should be used to diagnose sinusoidal obstruction syndrome, considering three degrees of certainty: probable, clinical and histologically proven (Table 9) **(LoE 3, strong recommendation).**	100%
Defibrotide is recommended when SOS is severe to improve survival **(LoE 3, strong recommendation)**, and can be considered when sinusoidal obstruction syndrome is moderate **(LoE 3, weak recommendation).** Early initiation after the diagnosis of sinusoidal obstruction syndrome may be preferable **(LoE 3, weak recommendation).**	100%, 96%, 100%
In patients with severe or very severe sinusoidal obstruction syndrome following HSCT, TIPS may be considered in case of rapid clinical deterioration despite medical treatment, including defibrotide, to improve outcomes **(LoE 4, weak recommendation).**	100%
In patients with very severe sinusoidal obstruction syndrome following HSCT, LT may be discussed in patients with a favourable haematological prognosis **(LoE 5, weak recommendation).**	100%
Patients with sinusoidal obstruction syndrome following HSCT can develop intrahepatic non-cirrhotic portal hypertension in the long-term **(LoE 5).**	100%
Follow-up including liver blood tests and imaging may be considered. First follow-up may be 3 to 6 months after initial diagnosis, with subsequent follow-up visits at longer intervals, if liver status remains stable **(LoE 5, weak recommendation).**	100%
In patients receiving oxaliplatin-based chemotherapy, or other drugs less commonly associated with sinusoidal obstruction syndrome development (Box 1), the following signs should raise a suspicion of SOS: contrast-enhanced CT or MRI showing perfusion abnormalities including mosaic enhancement pattern on late arterial phase or on portal venous phase, development of signs of portal hypertension, liver blood test abnormalities **(LoE 4, strong recommendation).**	100%
As these signs are not specific, liver biopsy is recommended to make a diagnosis of sinusoidal obstruction syndrome in this setting **(LoE 4, strong recommendation).**	100%
Drugs associated with sinusoidal obstruction syndrome development should be stopped whenever possible. No recommendation can be made in favour or against the use of defibrotide in this setting **(LoE 5, weak recommendation).**	100%
TIPS may be considered in cases of severe complications of portal hypertension **(LoE 5, weak recommendation).**	100%
In contrast to adults, defibrotide should be initiated as soon as sinusoidal obstruction syndrome is suspected in children, regardless of severity, as this treatment may improve outcomes **(LoE 4, strong recommendation).**	100%
CT is recommended over ultrasound to diagnose and plan treatment of splanchnic artery aneurysms **(LoE 4, strong recommendation).**	100%
The CT protocol should be multiphasic and include non-contrast, arterial phase, and portal venous acquisition with thin reconstruction enabling adequate reconstruction **(LoE 4, strong recommendation).**	100%
Work-up for risk factors for splanchnic artery aneurysm development should search for: (i) signs of portal hypertension, which increases the risk of true aneurysms; (ii) arterial anomalies and aneurysms in other sites, as they suggest an arterial wall disease; and (iii) factors responsible for pseudoaneurysm including trauma, surgery, local infection or inflammation **(LoE 3, strong recommendation).**	100%
Work-up should assess the risk of rupture of these aneurysms to guide therapeutic strategy by: (i) analysing splanchnic artery aneurysm morphological characteristics, including size and location, using contrast-enhanced CT; (ii) identifying patients with a higher risk of rupture, namely pregnant women and LT candidates; and (iii) searching for factors responsible for pseudoaneurysm (trauma, surgery, local infection or inflammation), since the risk of rupture of splanchnic artery aneurysms is higher in pseudoaneurysm than in true aneurysm **(LoE 3, strong recommendation).**	100%
Treatment decisions should be guided by the size, location and type of splanchnic artery aneurysms (true *vs.* pseudoaneurysm) (Fig. 5) **(LoE 3, strong recommendation).**	100%

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Appendix. (*continued*)

Recommendation/statement	Consensus
In patients with small (below 2–2.5 cm in the largest axis), asymptomatic, true splanchnic artery aneurysms, conservative treatment is recommended. First follow-up contrast-enhanced CT should be performed 6 months to 1 year after initial diagnosis and subsequently every 3 years if size remains stable **(LoE 4, strong recommendation).**	100%
In patients with symptomatic or large (above 2–2.5 cm in the largest axis) or fast-growing true splanchnic artery aneurysms, and in all patients with splanchnic pseudoaneurysms (high risk of rupture), interventional treatment is recommended **(LoE 4, strong recommendation).**	100%
In patients with splenic aneurysm of any size, interventional treatment is recommended in women of child-bearing potential and in LT candidates, as the risk of rupture is high **(LoE 4, strong recommendation).**	100%
In patients with gastro and/or peripancreatic aneurysms related to celiac axis occlusion, interventional treatment is recommended **(LoE 4, strong recommendation).**	100%
In patients with splanchnic artery aneurysms and an indication for interventional treatment, endovascular treatment should be proposed over open surgery, as it is associated with similar mortality but reduced morbidity. Open surgery is indicated when the endovascular approach is not feasible **(LoE 3, strong recommendation).**	100%
Management should be the same in children as in adult patients **(LoE 4, strong recommendation).**	100%
Both Doppler ultrasound and contrast-enhanced CT are useful to establish diagnosis and may be complementary in equivocal situations **(LoE 4, strong recommendation).**	100%
Contrast-enhanced CT also provides information on the presence or not of extrahepatic arteriovenous fistula and should be used for treatment planning **(LoE 4, strong recommendation).**	100%
Work-up for risk factors should include searching for: (i) a history of liver biopsy or surgery, liver interventional radiology, or liver trauma; (ii) features suggesting haemorrhagic telangiectasia, particularly in case of multiple fistulae; (iii) features suggesting liver malignancy; and (iv) features suggesting chronic liver disease in case of arterio-portal shunts **(LoE 4, strong recommendation).**	97%
In patients with hepatic arteriovenous fistula without related symptoms, a conservative approach is recommended **(LoE 4, strong recommendation).**	100%
In patients with hepatic arteriovenous fistula with related symptoms, without HHT, closure at the time of diagnosis is recommended **(LoE 4, strong recommendation).**	97%
In patients with isolated hepatic arteriovenous fistula requiring treatment, endovascular closure is the method of choice, while surgery may be an exceptional option for recurrent fistula despite repeated endovascular procedures **(LoE 4, strong recommendation).**	100%
Outside the HHT setting, there is no evidence to support the use of adjuvant medical therapy to reduce risk of recurrence **(LoE 5).**	100%
The general approach to diagnosis and management in children should follow that in adults. However, there are two important differences to consider: ◦ (i) rule out congenital haemangioma, which is managed medically **(LoE 3, strong recommendation, consensus)**; ◦ (ii) use caution with volume of embolic agent in infants owing to the risk of migration **(LoE 5, strong recommendation).**	100%
Surveillance for gastro-oesophageal varices is recommended when clinical, ultrasonographic, liver or spleen elastography data or platelet count suggest the presence of portal hypertension. Interpretation of these parameters can vary according to the type of vascular liver disease **(LoE 5, strong recommendation).**	100%
If no varices are observed at index endoscopy, the next endoscopy should be performed 2 years later. If small varices are observed at index endoscopy, the next endoscopy should be performed 1 year later (Fig. S3) **(LoE 5, strong recommendation).**	100%
NSBBs or endoscopic treatment are recommended in primary prophylaxis for portal hypertension-related bleeding, and both in secondary prophylaxis, to reduce morbidity and mortality **(LoE 3, strong recommendation).**	100%
In patients with refractory portal hypertension-related bleeding, TIPS is recommended **(LoE 3, strong recommendation).**	100%
In patients with recent PVT without cirrhosis, direct oral anticoagulants are suggested as an alternative to low-molecular-weight heparin and/or vitamin K antagonists, during the first 6 months after PVT diagnosis, to reduce morbidity and mortality **(LoE 3, weak recommendation).**	100%
In patients with chronic PVT without cirrhosis (*i.e.* >6 months after recent PVT diagnosis or portal cavernoma), direct oral anticoagulants may be preferred over vitamin K antagonists to facilitate adherence and improve safety **(LoE 2, weak recommendation).**	100%
In patients with Budd-Chiari syndrome, direct oral anticoagulants may be considered as an alternative to low-molecular-weight heparin and/or vitamin K antagonists to reduce morbidity and mortality, when liver function is preserved **(LoE 4, weak recommendation).**	100%
Intrauterine devices, mechanical contraception and microprogestatives are associated with a lower risk of thrombotic events and should be preferred over oestrogen-containing oral contraceptives **(LoE 3, strong recommendation).**	100%
Specific drugs known to be associated with vascular liver disorder development (Table 11) should be avoided or discontinued to avoid further progression of the disease **(LoE 4, strong recommendation).**	100%
Drugs associated with DILI (Table S2) may be used with caution to minimise adverse events, although there is no data to suggest a differential course of DILI in these patients. If used, regular monitoring of liver blood tests is suggested **(LoE 5, weak recommendation).**	100%
In patients with vascular liver diseases and impaired liver function and/or portosystemic shunting, certain drugs which have a high first-pass effect, depend on albumin binding or are metabolised by the liver (Table 12) may be used with caution or avoided **(LoE 5, weak recommendation).**	100%
In patients with vascular liver diseases of childbearing age, advice on pregnancy should be offered early after liver disease diagnosis. Pregnancy should be planned when the liver disease and the prothrombotic condition are well-controlled **(LoE 3, strong recommendation).**	100%
In patients with vascular liver diseases and myeloproliferative neoplasm, cytoreductive therapy should be stopped before conception as it is teratogenic **(LoE 3, strong recommendation).**	96%

(*continued on next page*)

Appendix. (*continued*)

Recommendation/statement	Consensus
Vitamin K antagonists or direct oral anticoagulants should be switched to low-molecular-weight heparin as soon as pregnancy is confirmed and at least before the 4th week of gestation. In this setting, low-molecular-weight heparin should then be continued during the whole pregnancy **(LoE 3, strong recommendation).**	96%
In patients with vascular liver diseases not receiving anticoagulants, prophylaxis of thromboembolic events using low-molecular-weight heparin may be considered for 6 weeks after delivery to prevent thrombotic events **(LoE 5, weak recommendation).**	96%
In patients with vascular liver diseases, gastroesophageal varices should ideally be searched for in the year before conception, or during the second trimester of pregnancy if not done before conception **(LoE 4, strong recommendation).**	100%
In patients with vascular liver diseases, variceal haemorrhage occurring during pregnancy should be prevented and managed as in non-pregnant patients **(LoE 4, strong recommendation).**	100%
Vaginal delivery should be preferred over caesarean section, even in cases of portal hypertension. Caesarean section should be reserved for obstetrical indications **(LoE 4, strong recommendation).**	100%
Platelet count >20x10^9/L and >50x10^9/L should be considered as safe for vaginal delivery and caesarean section, respectively. Platelet count >75x10^9/L should be considered safe for epidural anaesthesia and >50x10^9/L for spinal anaesthesia **(LoE 5, strong recommendation).**	100%
Oestrogen-derived oral contraceptives should not be administered post-partum **(LoE 5, strong recommendation).**	100%
Treatment with beta-blockers and warfarin is possible during breastfeeding, while other vitamin K antagonists or direct oral anticoagulants are contraindicated **(LoE 4, strong recommendation).**	100%
Systematically assessing the psychological and social impact of the disease is recommended to identify issues and refer patients to dedicated professionals and patient associations **(LoE 5, strong recommendation).**	100%
Initial and follow-up management requires a multidisciplinary team including at least hepatologists, pathologists, radiologists, interventional radiologists, haematologists and/or vascular physicians, and liver surgeons. The centre should have expertise in TIPS placement, portal vein recanalisation, LT and in critical care management of patients with liver disease **(LoE 5, strong recommendation).**	100%

Abbreviations

AFP, alpha-fetoprotein; ALF, acute liver failure; ALT, alanine aminotransferase; APF, arterio-portal fistulae; AVMs, arterio-venous malformations; BCS, Budd-Chiari syndrome; CPG, Clinical Practice Guidelines; DOACs, direct-acting oral anticoagulants; EASL, European Association for the Study of the Liver; EBMT, European Society for Blood and Marrow Transplantation; FNH, focal nodular hyperplasia; HAVF, hepatic arteriovenous fistulae; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HHT, hereditary haemorrhagic telangiectasia; HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; HVPG, hepatic venous pressure gradient; INR, international normalised ratio; IVC, inferior vena cava; LDH, lactate dehydrogenase; LMWH, low molecular weight heparin; LoE, level of evidence; LSM, liver stiffness measurement; LT, liver transplant(ation); MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; NO-SD, non-obstructive sinusoidal dilatation; NSBB, non-selective beta-blockers; PH, portal hypertension; PI, prognostic indices; PNH, paroxysmal nocturnal hemoglobinuria; PROs, Patient-Reported Outcomes; PSVD, portosinusoidal vascular disorder; PVR, portal vein recanalisation; PVT, portal vein thrombosis; RCT, randomised controlled study; RR, relative risk; SAA, splanchnic artery aneurysms; SD, sinusoidal dilatation; SMV, superior mesenteric vein; SOS, sinusoidal obstruction syndrome; SVR, sustained virological response; TACE, transarterial chemo-embolisation; TIPS, transjugular intrahepatic portosystemic shunt; UDCA, ursodeoxycholic acid; VKA, vitamin K antagonists; VOD, veno-occlusive disease.

Conflict of interest

PE reports research funding from Terrafirma; consulting fees from Mursla, Genfit, Boehringer Ingelheim, Cook, AstraZeneca, Jazz and Abbelight; speaker fees from AbbVie, Genfit. LM reports no conflicts of interest. VHG reports no conflicts of interest. WA reports honoraria from AstraZeneca, Bayer, BMS Pfizer, Sanofi, Viatris; participation on advisory boards for AstraZeneca, Bayer, Sanofi, Norgine, Viatris. MG reports no conflicts of interest. JCG-P reports grants from Mallinckrodt, Cook Medical, Gore medical; consulting fees from Cook Medical, AstraZeneca, Gore medical, GSK; honoraria from Gore medical, Cook medical. SDM reports no conflicts of interest. VM reports consulting fees from Mirum Pharmaceuticals, Albireo, AstraZeneca; speaker fees for Albireo. DT reports speaker fees from WL Gore & Associates. VV reports no conflicts of interest.

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

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Supplementary data

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