Diagnosis and Therapy of Visceral Vein Thrombosis: An Update Based on the Revised AWMF S2k Guideline

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Abstract

Splanchnic or visceral vein thromboses (VVTs) are atypical thrombotic entities and include thrombosis of the portal vein, hepatic veins (Budd-Chiari syndrome), mesenteric veins, and splenic vein. All VVTs have in common high 30-day mortality up to 20% and it seems to be difficult to diagnose VVT early because of their rarity and their wide spectrum of unspecific symptoms. VVTs are often associated with myeloproliferative neoplasia, thrombophilia, and liver cirrhosis. VVT is primarily diagnosed by sonography and/or computed tomography. In contrast to venous thromboembolism, D-dimer testing is neither established nor helpful. Anticoagulation is the first-line therapy in patients with stable circulation and no evidence of organ complications. Anticoagulation improves significantly recanalization rates and stops the progress of thrombosis. Low-molecular-weight heparin, vitamin K antagonists, as well as direct-acting oral anticoagulants are possible anticoagulants, but it is noteworthy to be aware that all recommendations supporting the off-label use of anticoagulants are based on poor evidence and consist predominantly of case series, observational studies, or studies with small case numbers. When choosing a suitable anticoagulation, the individual risk of bleeding and thrombosis must be weighted very carefully. In cases of bleeding, bowel infarction, or other complications, the optimal therapy should be determined on a case-by-case basis by an experienced multidisciplinary team involving a surgeon. Besides anticoagulation, there are therapeutic options including thrombectomy, balloon angioplasty, stenting, transjugular placement of an intrahepatic portosystemic shunt, liver transplantation, and ischemic bowel resection. This article gives an overview of current diagnostic and therapeutic strategies.

Keywords

- splanchnic vein thrombosis
- portal vein thrombosis
- Budd-Chiari syndrome
- mesenteric vein thrombosis
- anticoagulation

Introduction

Splanchnic or visceral vein thromboses (VVT) belong to atypical thrombotic entities and include thrombosis of the portal vein (PVT), hepatic veins (Budd-Chiari syndrome [BCS]), mesenteric veins (MesVT), and splenic vein (SplVT). The most frequently affected vessel is the portal vein with an incidence of 2 to 3 per 100,000 persons-year. In most cases, the underlying cause of PVT is liver cirrhosis. PVT without cirrhosis, MesVT, SplVT, and BCS, by contrast, is rare. The incidence of noncirrhotic PVT or BCS in the European population is reported with approximately 0.1 to 0.2 per 100,000 persons-year. In comparison, the annual incidence of isolated MesVT is 1 per 100,000.[1] Patients with PVT die

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Table 1 Symptoms of visceral vein thrombosis

Symptom [%]	PVT	BCS	MesVT	SplVT
Asymptomatic	21	15	10	**70**
Abdominal pain	40	**64**	**63**	**57**
Acute abdomen	12	4	**47**	15
GIT bleeding	**28**	11	20	**29**
Ascites	31	**71**	11	11
Varices	**35**	18	7	18
Fever	13	9	8	10
Icterus	13	16	4	11
Encephalopathy	9	9	3	7
Nausea	13	16	16	23
Diarrhea	2	8	7	8

Abbreviations: BCS, Budd-Chiari syndrome; GIT, gastrointestinal; MesVT, mesenteric vein thrombosis; PVT, portal vein thrombosis; SplVT, splenic vein thrombosis.
Note: Predominating symptoms of each visceral vein thrombosis type are highlighted (based on data from Thatipelli et al).[3]

predominantly from bleeding complications, cirrhosis, and hepatocellular carcinoma; patients with BCS die from liver failure; and patients with MesVT die from infarctions of the bowel. The 30-day mortality rate is high with up to 20%, and in case of MesVT it reaches even up to 60%.[2,3] Triggers of VVT can be divided into local and systemic ones: the most important local reasons are liver cirrhosis and malignancies, followed by infectious or inflammatory abdominal processes (e.g., cholecystitis, pancreatitis, appendicitis, liver abscess, inflammatory bowel disease) as well as surgical procedures (e.g., bariatric interventions, splenectomy). Systemic conditions include predominantly myeloproliferative malignancies such as polycythemia vera or essential thrombocythemia, which account for 30 to 40% of VVT without cirrhosis or other malignancy. Hereditary thrombophilia, antiphospholipid syndrome, and other classic thrombotic risk factors have also been described.[4,5] Nevertheless, in about 25 to 30% of VVT, the etiology remains unclear.[6]

Pathophysiology and Clinical Symptoms

Delayed Diagnosis

It takes between 3 and 18 days from the onset of VVT symptoms until defining the diagnosis (average: 7 days); every 5th patient with VVT dies in the acute stadium of the thrombosis, and not seldom because of delayed diagnosis.[2,7] The most common symptoms are abdominal pain, gastrointestinal bleeding, and ascites. However, there is no specific or typical symptom for each VVT. Symptoms and signs can overlap between the different types of VVT. ►**Table 1** gives an overview; the predominating symptoms of each VVT type are highlighted.

Risk Factors, Pathophysiology, and Complications

PVT occurs as an isolated thrombosis or in combination with SplVT. PVT risk factors are divided into systemic (50–70%) and local (20–30%). Systemic risk factors include thrombophilia, myeloproliferative malignancies, Behçet's disease, paroxysmal nocturnal hemoglobinuria (PNH), as well as common risk factors of thrombosis-like hormonal contraceptives, pregnancy, and others. Typical local risks are liver cirrhosis, hepatic or abdominal tumors, intra-abdominal inflammations (e.g., pancreatitis, cholecystitis, appendicitis, inflammatory bowel disease, hepatitis), and surgical interventions.[8,9] The consequence of an acute occlusion of the PVT is intestinal congestion caused by reduced mesenteric drainage, which leads to colic-like pain, fever, and sometimes ileus. Without spontaneous or therapeutic recanalization, the PVT passes into a chronic stage, where collaterals assume the function of the occluded portal vein. Paraportal collaterals are described as cavernous transformation (►**Fig. 1**), portosystemic collaterals, and gastric or esophageal varices. These varices are the most common cause of bleeding as a consequence of portal hypertension. It is important to know that nontreated PVT can alternate between spontaneous recanalization and thrombotic occlusion. However, PVT associated with cirrhosis is explained by the delayed inflow of portal venous blood into the fibrotic liver tissue. The most frequent clinical sign in this case is ascites; cavernous transformation is uncommon.

Abdominal pain and ascites are the dominating symptoms of BCS and are explained by thrombosis of the entire liver veins with imminent acute liver failure. The reason for the high mortality rates of MesVT is explained by bowel infarctions.

Diagnostic Strategies

Imaging First

In contrast to diagnostic algorithms of venous thromboembolism, D-dimer testing is not part of the VVT diagnostic pathway. Most of the aforementioned circumstances lead to an elevation of D-dimer, which therefore is unspecific and not helpful. When anamnestic information, risk factors, or clinical signs support the suspicion of a VVT, diagnosis

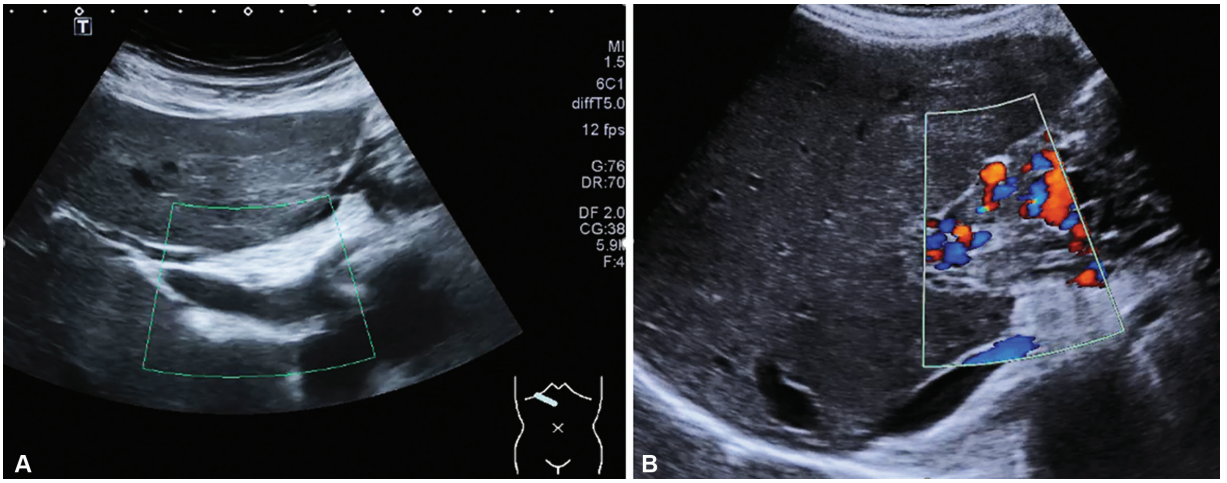

Fig. 1 (A) Acute portal vein thrombosis. (B) Chronic portal vein thrombosis with cavernous transformation. Many tortuous collateral vessels meander around the occluded portal vein (with kind permission of Prof. Thomas Karlas, Gastroenterology, University of Leipzig).

should be confirmed primarily by sonography and/or computed tomography (CT) angiography without any delay. Any unexplained abdominal pain should be investigated by imaging within 24 hours.

The abdominal sonography with color-coded duplex allows the differentiation between acute and chronic stage of PVT and gives answer to the question whether cirrhosis is present or not. Sonography shows a high sensitivity (89–93%) and specificity (92–99%) for detecting PVT. Contrast-enhanced CT and magnetic resonance imaging (MRI) can be used to further confirm the diagnosis and to search for malignancies, especially hepatocellular carcinoma. CT and MRI sensitivity can be reduced in PVT patients with cirrhosis when contrast agent flows so slowly that a PVT is feigned. Other false-positive findings can be caused by tumor compression or infiltration of the portal vein and contrast medium artifacts as well.[10] In this situation, contrast-enhanced sonography is recommended to distinguish between tumor infiltration or compression and thrombus. The same recommendation is given to all patients with incidental thrombosis in the portal and mesenteric veins seen in cross-sectional imaging, to reassess them before starting anticoagulation.

Sonography is also the primary imaging technique for BCS diagnosis with a sensitivity and specificity of approximately 85 to 90%.[11,12] The sonographic diagnosis requires a confirmation by CT or MRI diagnostics including the search for hepatocellular malignancies. A liver biopsy may be helpful only when smaller intrahepatic veins are affected, or other hepatic conditions should be excluded.[11,13]

In contrast to PVT and BCS diagnostics, cross-sectional imaging is superior to sonography in patients with MesVT. The sensitivity of sonography for detecting MesVT of 70 to 90% is not high enough, explained by the fact that it is often difficult to visualize mesenteric veins by sonography. Here, MR venography convinces with a sensitivity and specificity of nearly 100%. CT achieves a sensitivity of 91 to 95% and a specificity of 94 to 100% and should be prioritized, as it is ubiquitously available, and also allows the concomitant assessment of the bowel for ischemic signs.[12,14] For this reason, it is crucial to run both an arterial and portal venous phase. Signs of acute bowel ischemia are wall thickening or dilatation as well as intestinal and portal venous gas inclusions.[14]

In case of PVT with cirrhosis, esophagogastroscopy should be performed to evaluate the extent of gastric and esophageal varices as an important bleeding source.

Mandatory Screening for Myeloproliferative and Thrombophilic Disorders

PVT without cirrhosis, BCS, SplVT, as well as MesVT should draw attention to screen for malignancies, especially myeloproliferative neoplasia-like essential thrombocythemia, polycythemia vera, and primary myelofibrosis, as well as inherited and acquired thrombophilia disorders (e.g., factor V Leiden, prothrombin gene G20210A mutation, protein C and S deficiency, antithrombin deficiency, antiphospholipid syndrome).[5,15,16] Myeloproliferative diseases account for 30 to 40% of VVT cases without concomitant cirrhosis or other malignancy. It is recommended to screen for a mutation of JAK2-V617F, which is detectable in approximately 95% of polycythemia vera and in 40 to 50% of essential thrombocythemia. Screening for JAK2 mutations in patients with VVT can diagnose a myeloproliferative disorder in about 15% of cases before typical changes of blood cell count occur.[4] Therefore, it is assumed that VVT acts as an early manifestation of myeloproliferative malignancies, as a kind of early warning. In JAK2-V617F-negative patients, an extended hematological workup with screening for calreticulin mutations or bone marrow biopsy should be done.

VVT is also often described in patients with PNH, Behçet's disease, and autoimmune diseases.[8,9] Hormonal factors, especially hormonal contraception, hormonal replacement therapy, and pregnancy or postpartum, can increase the VVT risk. As in other thrombosis manifestations, VVT is often triggered by several interacting factors. Nevertheless, in approximately 25 to 30% of VVT cases, the etiology remains unclear.[6]

Asymptomatic, Incidental, and Chronic VVT

Approximately 10 to 25% of VVT cases are asymptomatic and are detected as incidental findings when abdominal imaging is performed for other reasons.[17] Without clinical symptoms, it is difficult to distinguish between acute and chronic thrombosis. Due to the fact that the probability of recanalization decreases with delayed initiation of anticoagulation, it should be determined whether the thrombosis is fresh or not.[11,18] But usually, this question cannot be answered for sure. Unless in case of PVT, when varicose dilatation of paraportal veins (cavernous transformation) is detected, chronic PVT can be assumed.

In all cases of VVT, both the extent of thrombosis and preexisting risk factors or comorbidities should be documented carefully, because the identification of etiological risk factors has important implications for further therapeutic decisions.

Treatment of VVT

Therapeutic anticoagulation is the first-line therapy in stable patients with acute and symptomatic PVT, MesVT, and BCS.[12] Anticoagulation prevents the progression of thrombosis, minimizes the risk of organ complications such as intestinal infarction and liver failure, and allows the recanalization of VVT to prevent the development of portal hypertension as a consequence of persistent thrombotic occlusion.[11] Before starting anticoagulation, some questions have to be answered: Is the patient in a stable or unstable clinical condition? Does the patient suffer from impaired liver function? Is the VVT in an acute or chronic stage? Is the VVT an incidental, asymptomatic finding?

Acute Symptomatic VVT, Critical and Unstable Conditions

In approximately 5% of all patients with VVT, clinical deterioration occurs within the first few days, despite anticoagulation. If there are any clinical signs of acute bowel ischemia or infarction, peritonitis, or perforation, open-surgical exploration, possibly with bowel resection, is required.[14] Patients with BCS are at high risk for acute liver failure. Endovascular strategies like local thrombolysis, thrombectomy, balloon angioplasty, and stenting, as well as transjugular placement of an intrahepatic portosystemic shunt (TIPS) or liver transplantation must be considered if organ complications are imminent.[2,11,19–21] Patients in unstable condition with hypotension, shock, high lactate levels, or gastrointestinal bleeding should be immediately evaluated by a multidisciplinary team consisting of experienced internists, vascular specialists/angiologists or radiological interventionalists, and surgeons to determine the optimal therapy strategy on a case-by-case basis. Endovascular strategies, TIPS or liver transplantation, are therapeutic options if anticoagulation alone is not promising. In cases of unstable conditions, especially in patients with acute MesVT, it may be reasonable to initially use unfractionated heparin due to its shorter half-life and better controllability, as long as no decision has been taken as to whether laparotomy or endovascular therapy must be performed in the case of impending or actual intestinal infarction.

Acute Symptomatic VVT, Stable Conditions without Organ Complications

In all other situations of acute VVT, stable circulation, and no evidence of organ complications such as intestinal infarction, liver failure, or gastrointestinal bleeding, therapeutic anticoagulation with a parenteral anticoagulant or a direct oral anticoagulant should be initiated as first-line therapy. After the initial phase low-molecular-weight heparin (LMWH), direct-acting oral anticoagulants (DOACs) or vitamin K antagonists (VKAs) can be used. International guidelines recommend a minimum therapy duration of 3 to 6 months for symptomatic thrombosis.[11,12,14,22] Six-month anticoagulation therapy may be insufficient to achieve portal vein recanalization in some cirrhotic patients with PVT. For such patients, the duration of anticoagulation should be prolonged to 12 months.[23] Discontinuation of the anticoagulation after 3 to 6 months may be considered in patients with VVT triggered by a clear transient risk factor, which is no longer present at the scheduled discontinuation of anticoagulation, and with a low risk of thromboembolic recurrence.[22] In a prospective registry study, the recurrent risk of thrombosis for patients with VVT associated with a transient trigger was 3.2% per year, while patients with persistent risk factors (e.g., cirrhosis) had a significantly higher risk of recurrent thrombosis of 11.3% per year.[6]

Anticoagulation should be continued indefinitely in cases of spontaneous thrombosis without detectable triggers, persistent risk factors, recurrent thrombosis, BCS, intestinal ischemia, or MesVT, as well as in patients with liver cirrhosis who are candidates for liver transplantation. There is currently no evidence for the efficacy of a dosage-reduced extended anticoagulation with apixaban or rivaroxaban analogous to the confirmed treatment options in extended secondary prophylaxis for patients with leg vein thrombosis or pulmonary embolism.

Incidental, Asymptomatic, and Chronic VVT

For asymptomatic PVT, which has presumably developed within the last few months, a therapy duration of at least 3 months is favored. By contrast, patients with chronic occlusion of the portal vein, cavernous transformation, and preexisting collaterals do not seem to benefit from anticoagulation, unless they suffered from MesVT or recurrent thrombosis, for which cases anticoagulation is recommended.[11]

Rebalanced Hemostasis

It should be noted that in patients with liver cirrhosis and impaired liver function, hepatic synthesis of most coagulation as well as fibrinolysis factors is impaired. Additionally, they present an altered platelet count secondary to portal hypertension. Altered routine tests (e.g., Quick/international normalized ratio [INR], activated partial thromboplastin time [aPTT], antithrombin) and thrombocytopenia may lead to the false assumption of "auto-anticoagulation."

Recent evidence is given that despite the presence of altered levels of factors involved in primary hemostasis, coagulation, and fibrinolysis, patients with stable cirrhosis have a rebalanced hemostatic system, which, however, can easily be altered by decompensation or infection, both in hemorrhagic and thrombotic direction.[24] Thus, it is important to emphasize that monitoring via aPTT, anti-Xa levels, or INR is only of limited merit. Standard laboratory coagulation tests are unable to predict bleeding risk and are inadequate for the assessment of the hemostatic status in these patients.[24] The feared bleeding risk, particularly with anticoagulants, is mainly determined by portal hypertension and esophageal varices, which should be treated, and much less by factor deficiency.

Efficacy and Safety of Anticoagulants

In a recent meta-analysis, VVT patients receiving anticoagulation were found to be at reduced risk of thrombus progression and recurrent thromboses (hazard ratio [HR]: 0.42; 95% confidence interval [CI]: 0.27–0.64) and mortality (HR: 0.23; 95% CI: 0.17–0.31).[25] In addition, anticoagulation for VVT is associated with higher recanalization rates and a lower risk of major bleeding in the long term.[25,26] The incidence of thromboembolic recurrence was 3.4% per 100 patient-years in anticoagulated patients. In contrast, patients who had discontinued their anticoagulation had a recurrence risk of 6.6, and patients who never received anticoagulation had a recurrence risk of 9.3 per 100 patient-years. The risk of major bleeding was lowest for anticoagulated patients (3.1 per 100 patient-years vs. 5.8 and 6.6, respectively), and so was mortality (5.7 per 100 patient-years vs. 23.3 and 21.8, respectively).[25] Two systemic reviews and meta-analyses also demonstrated an improvement in overall prognosis for anticoagulated VVT patients with cirrhosis: recanalization rates were significantly higher on anticoagulation, while mortality and risk of major bleeding were lower.[26,27] In a multicentric prospective registry study analyzing 604 VVT patients, patients with VVT triggered by a transient risk factor had the lowest recurrence risk (annual incidence: 3.2%; 95% CI: 1.4–7.0) and major bleeding (0.5% per year; 95% CI: 0.1–3.7).[6] Patients with cirrhotic PVT had the highest risk of major bleeding (10.0% per year; 95% CI: 6.6–15.1); however, patients with cirrhotic PVT also had the highest risk of recurrent thrombosis (11.3% per year; 95% CI: 7.7–16.8). Interestingly, cirrhotic PVT patients with anticoagulation showed significantly lower rates of spontaneous esophageal bleeding, which is explained by higher recanalization rates of PVT with the consequence of lower portal pressure.[28] Upon discontinuation of anticoagulation, about one-third of the patients suffer thrombosis recurrence.

Low-Molecular-Weight Heparin

The majority of patients considered in the meta-analyses discussed were treated with LMWH or LMWH followed by VKA. LMWH may offer advantages in cases of impaired liver function, as its effect is independent of hepatic metabolism and there is extensive experience with dosage modification in thrombocytopenia or high bleeding risk. LMWH is used at weight-adjusted dose for treatment without laboratory monitoring. Patients with obesity, renal insufficiency, or during pregnancy should be strictly monitored by regular clinical visits and should be advised to report immediately any sign that may be suggestive of an adverse event. Whether and how a dosage adjustment should be made has been discussed controversially.

Vitamin K Antagonist

Vitamin K antagonists should be used by laboratory monitoring with a target INR of 2.0 to 3.0. The limitations of the INR value in patients with cirrhosis should be kept in mind: the INR might or might not be representative of the real anticoagulation intensity and the results may vary between centers. In addition, the INR may easily be influenced by food and drugs, which further increases the difficulty in assessing the efficacy of VKA.

Direct-Acting Oral Anticoagulant

The extent to which DOAC represent at least an equivalent or superior therapy option compared to a sequential therapy of heparin and VKA, which was still favored in older guideline recommendations, cannot be conclusively assessed at present.[29] Cirrhotic patients and those with relevant liver insufficiency have been deliberately excluded from DOAC phase III trials and therefore limited data are available for these patients. DOAC might have some advantages over heparins or VKA; for example, they do not require dose-adjustment by laboratory tests, and thus the issue on the validity of the INR in this setting could be eliminated.[12] However, retrospective studies and a systemic review could not confirm the superiority of either therapy regime.[30] Due to low case numbers and heterogeneity of the individual studies, no comparison of the various anticoagulation regimes is possible; however, treatment with DOAC seems to be a therapeutic option in many cases of both noncirrhotic VVT and PVT on the ground of cirrhosis.[31] It could be advantageous that DOACs are subject to first-pass effect in the liver and therefore DOACs at high concentrations flow the portal venous pathway. By contrast, enteral absorption, which can be impaired particularly in the case of bowel ischemia, is to be regarded as disadvantageous.[29]

Depending on the severity of liver insufficiency, determined by Child-Pugh staging, ►Table 2 gives an overview of dosage and contraindications of oral anticoagulants according to current pharmacologic information.

Before and During Anticoagulation

Before deciding anticoagulation or upon initiation of anticoagulation therapy, the risk–benefit ratio for the individual patient should be carefully considered and documented. Risk factors for bleeding are esophageal varices if not treated prior to anticoagulation and severe thrombocytopenia. The cut-off value of severe thrombocytopenia remains controversial. Even though some studies have revealed that a platelet count of $<50 \times 10^9$/L increases the risk of bleeding in cirrhotic patients, others reported that the risk of bleeding was not increased in such patients.[32]

Table 2 EMA recommendations on oral anticoagulation in liver disease

	Warfarin	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Child-Pugh A	Possible	Possible	Possible	Possible	Possible
	Use with caution, if bleeding risk predominates	Use with caution, if ALAT/ASAT > 2 ULN or bilirubin >1.5 ULN	Not recommended, if ALAT/ASAT > 2 ULN	Use with caution, if ALAT/ASAT >2 ULN or bilirubin >1.5 ULN	Not recommended, if bleeding risk predominates
Child-Pugh B	Possible	Possible	Possible	Possible	Not recommended
	Use with caution, if bleeding risk predominates	Use with caution, if ALAT/ASAT > 2 ULN or bilirubin >1.5 ULN	Not recommended, if ALAT/ASAT > 2 ULN	Use with caution, if ALAT/ASAT >2 ULN or bilirubin >1.5 ULN	Not recommended
Child-Pugh C	Possible	Not recommended	Not recommended	Not recommended	Not recommended

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; EMA, European Medicines Agency; ULN, upper limit of normal.
Note: red means "not recommended", yellow means "use with caution", green means "possible treatment" (traffic light system)

An endoscopy of the upper gastrointestinal tract should be performed to look for signs of portal hypertension and ligate any esophageal varices. It is recommended to test and eradicate *Helicobacter pylori* to minimize the risk for mucosa lesions associated with *H. pylori* gastritis. Nonselective β-blockers should be used to reduce portal hypertension and thus the risk of bleeding.[33,34] Additionally, all VVT patients should receive concomitant therapy with proton pump inhibitors, especially in case of peptic ulcer disease.[35,36] All medications with potential bleeding risk, including over-the-counter medications, should be critically evaluated or stopped as appropriate and if possible (e.g., nonsteroidal anti-inflammatory drugs, antiplatelets, glucocorticoids, ginkgo). Alcohol cessation counseling should be provided.

The measurement of baseline liver and renal function, complete blood count, prothrombin time/INR, and activated partial thromboplastin time (with all discussed limitations) is still useful for follow-up to detect minor blood losses at an

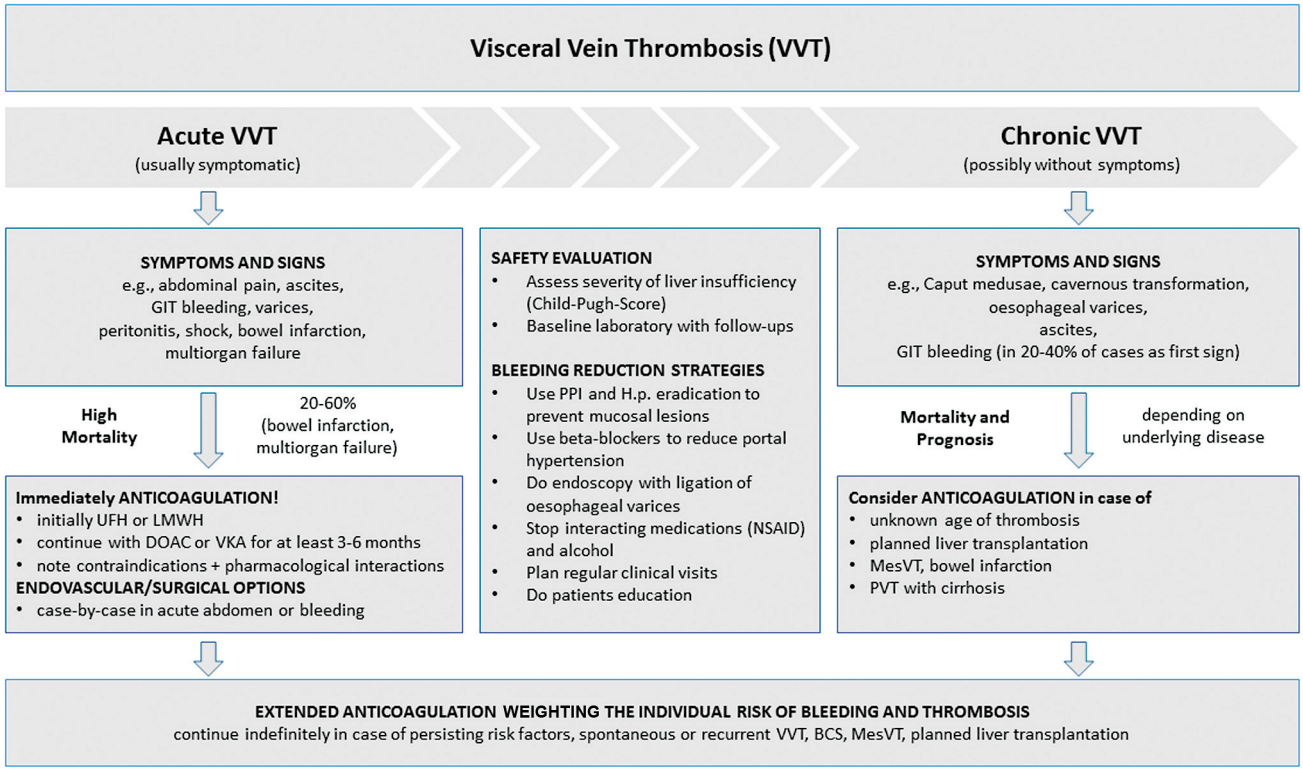

Fig. 2 Visceral vein thrombosis management according to clinical presentation. BCS, Budd-Chiari syndrome; DOAC, direct oral anticoagulants; GIT, gastrointestinal; H.p., *Helicobacter pylori*; LMWH, low-molecular-weight heparin; MesVT, mesenteric vein thrombosis; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor; PVT, portal vein thrombosis; UFH, unfractionated heparin; VKA, vitamin K antagonist; VVT, visceral vein thrombosis.

early stage and to ensure the correct dose-adjustment of all medications. VVT patients should be monitored by regular clinical visits, and educational information should be provided to report immediately any adverse event. ►Fig. 2 summarizes the algorithm for the main therapeutic aspects, considering the clinical course.

All these circumstances taken in account, the use of anticoagulants is safe, improves survival, and is not accompanied with higher bleeding rates in comparison to untreated patients.

Conflict of Interest

KSM got Honoraria for lectures from Bayer Health Care, BMS/Pfizer and Leo Pharma.

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