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CURRENT CLINICAL CONTROVERSY

Management of Non-tumoral Portal Vein Thrombosis in Patients with Cirrhosis

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Abstract

Non-tumoral portal vein thrombosis (PVT) remains a highly relevant topic in the field of hepatology and liver transplantation with much surrounding controversy. Although multiple studies have shown that PVT is associated with adverse outcomes with increased morbidity and mortality rates, others have not reported the same clinical impact of PVT, arguing rather that incident PVT reflects worsening portal hypertension and the natural history of the disease. Despite this uncertainly, PVT is a dilemma facing the clinician on a daily basis often requiring a multidisciplinary team-based approach between hepatologists, transplant surgeons, interventional radiologists and hematologists. In this review, the authors provide a summary of the evidence supporting best clinical practices in the management of non-tumoral PVT in patients with cirrhosis.

Abbreviations

AC	Anticoagulation
CTP	Child–Turcotte–Pugh
DOAC	Direct oral anticoagulant
INR	International normalized ratio
LMWH	Low molecular weight heparin
MELD	Model for end-stage liver disease
PT	Prothrombin time
PCC	Prothrombin complex concentrates
PVT	Portal vein thrombosis
SMV	Superior mesenteric vein
TIPS	Transjugular intrahepatic portosystemic shunt
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

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Introduction

Portal vein thrombosis (PVT) remains a controversial topic in the field of hepatology and liver transplantation and hepatic decompensation. Although multiple studies have shown that PVT is associated with adverse outcomes with increased morbidity and mortality rates [1, 2], others [3] have not reported the same clinical impact of PVT, arguing rather that incident PVT reflects worsening portal hypertension and the natural history of the disease rather than being a primary morbid event. Despite this controversy, it is clear that PVT is a dilemma facing the clinician on a daily basis. As liver transplant centers continue to develop increased comfort performing liver transplants in candidates with PVT, the experience of transplant hepatologists will only continue to grow, allowing for increased availability of accurate epidemiologic prevalence and incidence and post-transplantation outcomes. In this review, the authors will provide a summary of the evidence supporting the best clinical practices in the management of non-tumoral PVT in patients with cirrhosis.

Epidemiology and Definition

PVT and thrombosis of the mesenteric venous system are common in patients with cirrhosis [4]. Prevalence rates of PVT are largely dependent on the stage of cirrhosis where rates approach 1% in compensated cirrhosis versus upwards of 10% in decompensated cirrhosis [4]. Though several

Table 1 Yerdel grade for non-tumoral PVT

Grade	Description
1	< 50% PV occlusion ± minimal SMV extension
2	> 50% PV occlusion ± minimal SMV extension
3	Complete PV occlusion + complete proximal SMV occlusion; distal SMV is non-occluded
4	Complete occlusion of the PV, proximal and distal SMV

PV portal vein; *SMV* superior mesenteric vein

classification and definition schemes have been proposed, the most widely accepted is the Yerdel grade [5], which places PVT into one of the four grades depending on the involvement of one or both mesenteric veins and the degree of vascular occlusion (Table 1). For grade III–IV PVT, there is a significant risk of small bowel ischemia due to clot extension into the superior mesenteric vein (SMV) [6]. At present, the Yerdel grade is largely utilized for clinical research with little use in the clinic beyond surgical planning for liver transplantation. More recently, a new PVT classification was proposed by Sarin et al. [7] that has greater clinical utility, taking into account the site of PVT (Type 1: only trunk; Type 2: only branch; Subtypes 2a: one branch, and 2b: both branches; Type 3: trunk and branches), degree of portal venous system occlusion (occlusive vs. non-occlusive), duration (recent or chronic) and presentation (symptomatic vs. asymptomatic), extent of occlusion (splenic vein, SMV, or both), and type and presence of underlying liver disease (cirrhotic, non-cirrhotic, post-transplant, hepatocellular carcinoma, local malignancies, and associated conditions).

Risk Factors

The development of non-tumoral PVT in cirrhosis is related to Virchow's triad, where slow portal vein blood flow, endothelial injury with resultant dysfunction, and hypercoagulability all contribute to clot formation (Fig. 1) [8]. Slow or turbulent portal blood flow facilitates blood pooling in the portal venous system, leading to impaired thrombin breakdown and/or removal [8]. Doppler ultrasound studies suggest that for each cm/s the portal vein velocity decreases below 15 cm/s and there is a sixfold increase in de novo PVT development in the ensuing 12 months [9]. Established risk factors associated with slow portal vein blood flow include age, gender, non-selective beta-blocker use, portosystemic shunting (e.g., spontaneous splenorenal shunt), severity of liver disease (as defined by Child–Turcotte–Pugh [CTP] class), and splenectomy [9–11]. Moreover, patients with cirrhosis exhibit features of hypercoagulability with decreased levels of anti-hemostatic protein C, protein S, antithrombin III, and heparin cofactor II as well as elevated levels of pro-hemostatic factor VIII [12]. While more extensive data exist for patients with PVT in the absence of cirrhosis, both inherited and acquired hypercoagulable disorders appear to be more common in patients with cirrhosis where rates of antiphospholipid antibody syndrome, factor V Leiden, Janus kinase (JAK) 2V617F, methylenetetrahydrofolate reductase C677T, and prothrombin G20210A mutations may occur more commonly in patients with PVT [13, 14]. Current clinical guidelines [15] do not yet recommend universal screening for these disorders in all patients at risk of PVT; rather, consideration of consultation with a hematologist may be considered on a case-by-case basis. The etiology of underlying cirrhosis may also contribute to PVT development as patients with nonalcoholic steatohepatitis (NASH),

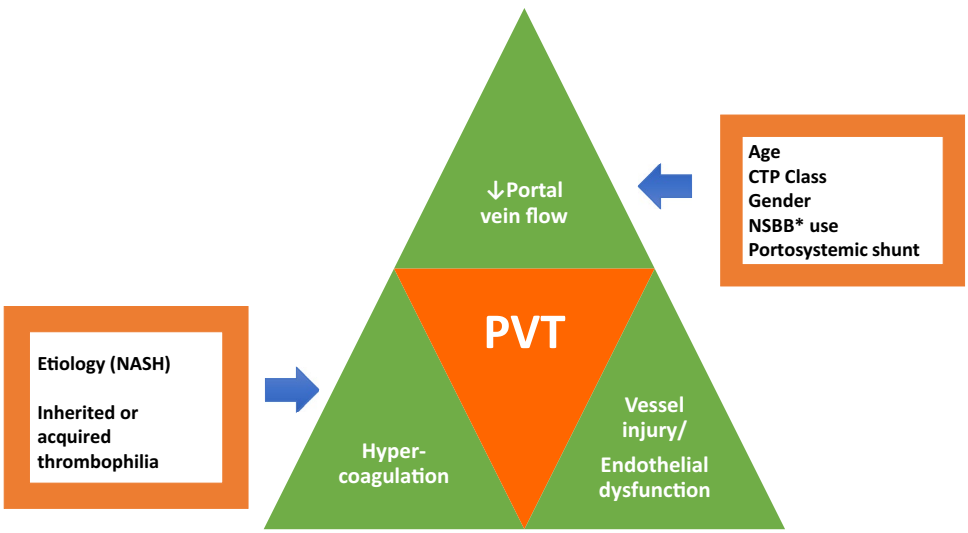

Fig. 1 Development of non-tumoral portal vein thrombosis (PVT) is related to the synergistic interaction between low portal vein blood flow, endothelial dysfunction, and hypercoagulability. Nonalcoholic steatohepatitis and inherited or acquired thrombophilia also increase the risk of PVT and compound hypercoagulability. *Nonspecific beta-blockers

autoimmune hepatitis, or autoimmune biliary disease appear to be predisposed [16, 17].

Screening and Diagnosis Confirmation

Although conflicting reports exist regarding the clinical implications of PVT, universal screening for PVT remains controversial, as the current best clinical practices which include routine screening ultrasound every 6 months to detect hepatocellular carcinoma in all cirrhosis patients though recent consensus guidelines [15] suggest performing simultaneous Doppler ultrasound. Less debate exists for the subset of patients who are eligible for liver transplantation, as PVT diagnosed prior to transplantation is associated with inferior post-transplantation outcomes, including lower survival [18]. As the surgeon must be able to perform a physiologic anastomosis or thrombectomy in order to restore portal flow to the graft, this is often impacted by the grade of thrombosis [19, 20]. With this rationale in mind, screening for PVT in liver transplant candidates is imperative so as to enable prompt diagnosis and detection [20]. Doppler ultrasound should be performed at a minimum of every 6 months. As Doppler ultrasound can be limited by significant operator variability, where the ability to discern the difference between thrombosis and absence of blood flow remains challenging and can negatively impact performance metrics with lower rates of sensitivity and specificity, confirmatory cross-sectional imaging with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan is recommended [21]. The extent of mesenteric vein involvement can be assessed with CT or MRI in addition to detecting the presence of the sequelae of chronic thrombosis (e.g., cavernoma, collateralization) or the presence of malignancy and associated tumor thrombus, offering additional clinically useful information beyond that provided by Doppler ultrasound [22].

Assessment Prior to Treatment Initiation

When considering treatment for PVT, either anticoagulation (AC) or transjugular intrahepatic portosystemic shunt (TIPS) may be considered. Patients with cirrhosis with a medical indication for therapeutic AC are a special patient population worthy of careful consideration. Prior to starting chronic AC, the patient with cirrhosis should be assessed for bleeding risk through careful history taking and physical examination. The history should include active alcohol dependence, active pathologic or unexplained gastrointestinal bleeding, a personal or family history of bleeding disorders, and recent intracranial hemorrhage. The examination should include an assessment of functional status (e.g., Karnofsky Performance Score, ECOG score, or Frailty Index). Routine laboratory measures should be obtained and reviewed including a complete blood count as platelet counts $<50\times10^9$/L independently predict bleeding events in cirrhotic patients treated with AC for PVT [23]. Prothrombin time–international normalized ratio (PT-INR) should *not* be routinely obtained as a part of the bleeding risk assessment as PT-INR is not an accurate predictor of bleeding risk in patients with cirrhosis [24, 25]. Prior to AC initiation, all patients should undergo screening upper endoscopy to assess for the presence of gastroesophageal varices. If medium–large varices and/or high-risk stigmata (e.g., red wale sign or platelet plug) are found, endoscopic therapy with band ligation every 2–4 weeks or pharmacologic treatment with non-selective beta blockade should be employed, following current guideline recommendations [26, 27]. When considering TIPS placement, standard contraindications should be sought including hepatic encephalopathy, advanced liver disease (e.g., CTP class C), and abnormal cardiac testing (e.g., right ventricular dilation or dysfunction).

Safety of AC

In general, treatment with AC should be considered in all patients with compensated cirrhosis (CTP class A or B). Although the currently available literature is limited both in scope and by retrospective study design with significant heterogeneity, AC appears to be a safe treatment for patients with cirrhosis and non-tumoral PVT. Multiple experiences have been published using vitamin K antagonists (VKA), low molecular weight heparin (LMWH), and direct-acting oral anticoagulants (DOAC) [28–32]. In terms of safety, the initial reports described major bleeding rates to be not only similar when comparing AC-treated and AC-untreated patients with PVT, but also to that of the AC-treated general medical population [33]. A recent meta-analysis of observational AC treatment trials published by Qi et al. [34] reported a pooled bleeding rate of all bleeding events (major and minor) of 3.3% for LMWH or VKA (95% CI 1.1–6.7%) when used for the treatment of PVT. Nevertheless, a recent retrospective study by La Mura et al. [32] of 223 subjects treated with VKAs ($n=63$ PVT, $n=160$ venous thromboembolism [VTE]) describes significantly higher rates of major bleeding in patients with cirrhosis and PVT treated with VKAs when compared with cirrhotic patients with VTE. Whether or not AC in and of itself is associated with greater rates of gastrointestinal hemorrhage also remains controversial; multiple reports describe no increased risk of variceal or non-variceal gastrointestinal bleeding in AC-treated versus untreated cirrhotic patients without PVT [32].

Table 2 Advantages and disadvantages of each modality of anticoagulation for non-tumoral PVT

Agent	Advantages	Disadvantages
Vitamin K antagonist (VKA)	Familiarity through extensive clinical use over many years	Unclear therapeutic goal in liver disease patients
	Low cost	Frequent monitoring with uncertain target levels
	Oral formulation	
	Reversal widely available	
Low molecular weight heparin (LMWH)	Safe and effective	Expense
	Familiarity	Subcutaneous injections
	Reversal widely available	Monitoring is also controversial (Xa level)
	Safe and effective	Expense
Direct oral anticoagulant (DOAC)	Oral formulation	Reversal agents not widely available
		Monitoring is also controversial (Xa level)

Choice of Anticoagulant

Since each anticoagulant has strengths and limitations, no absolute recommendation can be made in choosing one medication over another (Table 2). VKA, LMWH, or DOACs may all be considered in coordination with hematologic consultation. VKA is limited by the observation that patients with cirrhosis often have elevated baseline PT-INR values. Consequently, smaller doses of VKAs are required to obtain the consensus therapeutic window, which when combined with frequent careful monitoring inconveniences the patient and burdens the healthcare system. Model for end-stage liver disease (MELD) score inflation due to the artificially high INRs due to AC therapy is also of concern and may be used to "game" the transplant allocation prioritization system. Additionally, a recent report by La Mura et al. [32] suggests an increased rate of bleeding when VKAs are used to treat PVT in comparison with the use for treatment for VTE. LMWH is similarly limited in practicality, as daily injections require patient education combined with availability and proper storage of medical supplies. Furthermore, utilizing anti-factor Xa (anti-Xa) levels to guide dosing of LMWH is problematic in patients with cirrhosis since patients often fail to achieve desired therapeutic levels of anti-Xa with either prophylactic or therapeutic dosing [33]. Anti-Xa levels are inversely correlated with the severity of liver disease, due to variations in antithrombin, and are limited in CTP class B and C disease, in addition to being influenced by obesity, renal insufficiency, and pregnancy [33]. Although limited by their lack of widespread commercial availability, thrombin generation assays, which are independent of antithrombin and anti-Xa activity, offer a more reliable tool to determine treatment efficacy [34, 35]. DOACs, while widely used in cardiovascular and hematologic disease with favorable safety and efficacy profiles, are largely experimental in patients with cirrhosis and PVT, but are approved for use in early-stage CPT class A disease. While bleeding rates are similar when comparing DOAC used to treat PVT to the more traditional VKAs or LMWH [30], widespread adoption of DOACs has been slow. Patients with cirrhosis were largely excluded from the large-scale pre-marketing DOAC trials; furthermore, safety and efficacy data in CPT class C disease are still not available. In the USA, drug package inserts have variable warnings against the use in CPT class B or C disease. Unlike VKA, reversal agents are less readily available for the DOACs with idarucizumab approved for reversal of dabigatran [36] and andexanet alfa for apixaban and rivaroxaban [37]. A recent case report demonstrated successful reversal of dabigitran prior to liver transplantation without major bleeding or new thrombosis highlighting the practical use of this newly available reversal agent [38]. Prothrombin complex concentrates may be considered as an off-label surrogate for a direct reversal agent to normalize PT-INR while more widespread availability of reversal agents is awaited [39]. Most DOACs have a longer half-life than LMWH, with the exception of apixaban (which is similar to LMWH), increasing concern over a lack of a reversal agent that does not exist for LMWH. Commercially available drug levels of the Factor Xa inhibitors are expected in the near future in order to guide dosing; however, these are not yet widely available.

Efficacy of AC

In general, response rates are variable and range from 42 to 82% in terms of either a partial or a complete recanalization of the splanchnic veins [28, 31, 40]. Factors known to predict recanalization are time of onset of PVT (< 6 months from diagnosis of PVT-free imaging), early initiation of AC (< 3 months clot diagnosis), and the degree of thrombus (partial vs complete) [41]. Thrombosis recurrence after

discontinuing therapy for chronic PVT following clot resolution ranges from 27 to 38% [23]. Though the optimal duration of AC remains controversial, consensus opinion would suggest continuation of AC for 3–6 months after clot resolution unless there is a compelling indication for lifelong AC (e.g., SMV involvement, inherited or acquired thrombophilia, recurrent PVT). The role of indefinite secondary prophylaxis after clot resolution may be helpful in selecting individual circumstances and can be considered on a case-by-case basis, although the best clinical practices have yet to be established in this at-risk patient population.

Patient Selection

Patient-centered outcomes for PVT remain controversial with differing opinions regarding whether or not PVT is associated with higher morbidity and/or mortality [2] or rather if it simply is a reflection of the natural history of cirrhosis [42]. Furthermore, improved outcomes with AC for PVT in cirrhosis patients remain controversial as several studies suggest a benefit in preventing future hepatic decompensation [23, 43], whereas others do not [44, 45]. What is clear is that patients with PVT who undergo liver transplantation experience a more technically complex surgery, have more postoperative complications, have higher in-hospital mortality, and have inferior outcomes in terms of patient and graft survival, the most significant of which are seen with complete thrombosis of the main portal vein

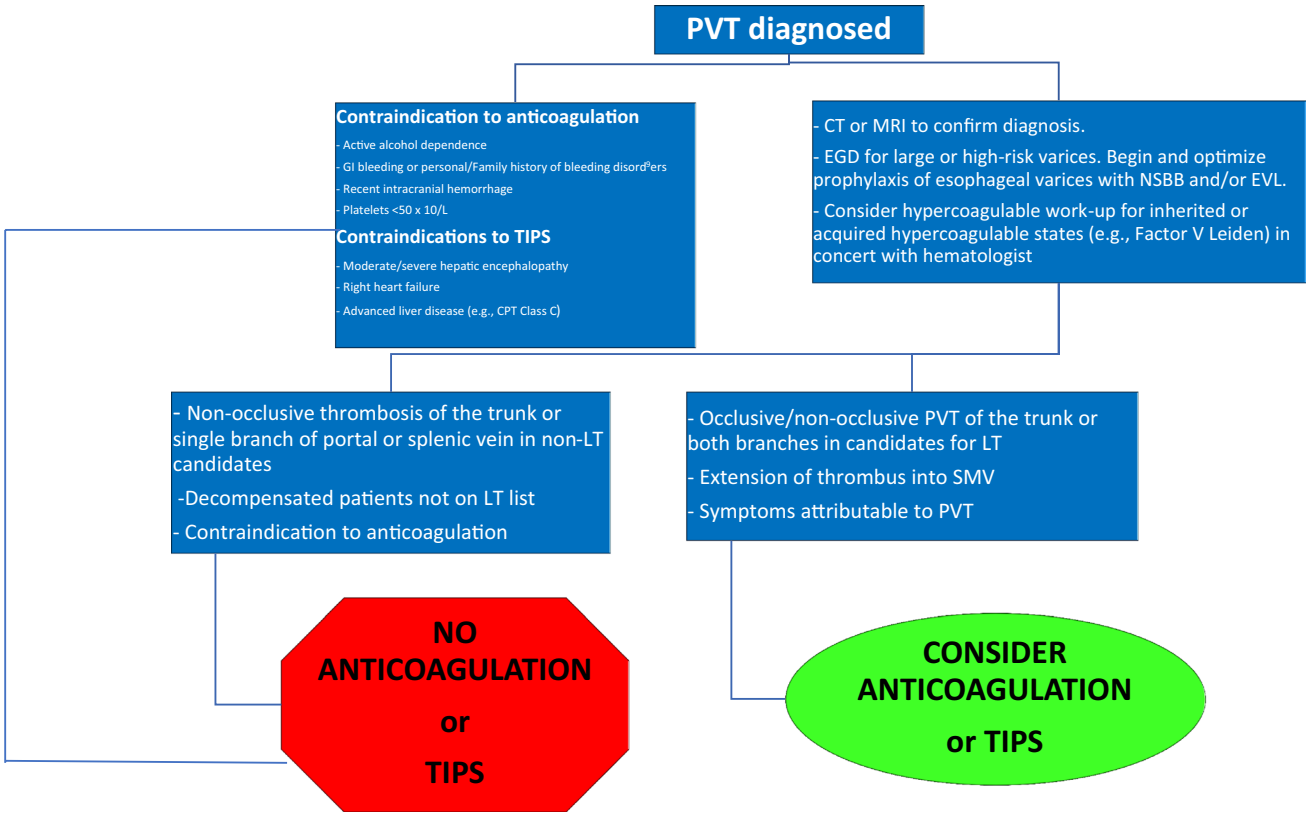

Fig. 2 Algorithm for clinical management of non-tumor portal vein thrombosis (PVT). Abbreviations: transjugular intrahepatic portosystemic shunt (TIPS); esophageal variceal ligation (EVL); non-selective beta-blocker (NSBB); liver transplant (LT); superior mesenteric vein (SMV); gastrointestinal (GI)

[5, 18]. Furthermore, pre-transplant PVT is associated with post-transplant vascular issues including early hepatic artery thrombosis and acute post-transplant PVT [46, 47]. Liver transplant recipients with PVT require significantly more transfusions of packed red blood cells during their operation, independent of AC status [5, 18]. Nonetheless, Yerdel grade 1 PVT liver transplant recipients have outcomes similar to recipients without PVT [5]. For these reasons, liver transplant candidates with occlusive main PVT with or without proximal extension into the SMV (Yerdel grade 2 or higher) should be prioritized for treatment with AC. Yerdel grade 2 PVT or higher in non-transplant candidates should also be considered for AC on an individualized basis where patients may derive benefit, especially in the presence of symptoms suggestive of or definitive for intestinal ischemia.

Role of TIPS

Although historically TIPS was considered to be contraindicated in patients with cirrhosis and PVT, more recent reports suggest that TIPS is in fact a safe and effective treatment for chronic PVT when performed in the presence of significant portal hypertension or symptomatic complete occlusion of the main portal vein [48]. Rates of recanalization are similar to or superior to those published for AC alone ranging from 60 to 92% depending on vascular access technique. TIPS can thus be considered an alternative equivalent to chronic AC [49]. TIPS is a technically challenging procedure in the presence of PVT and often requires a high-volume center with experience and expertise with this mechanical treatment for optimal results. Practically, although TIPS is often undertaken with concomitant AC and is often institution dependent, recent reports suggest that TIPS alone may be sufficient for recanalization with no immediate or chronic AC required in order to maintain stent patency [49, 50]. Whether or not AC or TIPS is utilized, the ultimate goal is for either to serve as a bridge to transplantation in order to maintain portal vein patency, enabling the surgical graft to be constructed. Figure 2 provides a suggested algorithm for pre-treatment assessment and treatment of the patient with cirrhosis and non-tumoral PVT.

Conclusions

Non-tumoral PVT is a highly prevalent condition with significant morbidity and mortality that occurs in part due to low portal vein blood flow, endothelial dysfunction, and hypercoagulability, the latter of which is affected by etiology of liver disease including NASH and inherited or acquired thrombophilia. The diagnosis of PVT is made with a combination of screening ultrasound and confirmatory cross-sectional imaging with CT or MRI scanning. Before treatment can be initiated with either AC or TIPS, a careful pre-intervention assessment for contraindications to AC or mechanical treatment with TIPS should be completed. No optimal class of AC has demonstrated superiority in the treatment of PVT, although bleeding rates appear to be acceptable for all of the commonly used agents. Since efficacy of AC and TIPS appears comparable, no recommendations can be made for or against either as the primary treatment for non-tumoral PVT. Future large-scale registry and interventional studies are needed to further clarify the natural history and treatment response of PVT in order to better understand the implication of the current best clinical practices summarized by this review.

Compliance with ethical standards

Conflict of interest Dr. Stine receives research support from TARGET Pharma, Inc. and serves as a consultant for Bayer, Inc. Dr. Northup has no financial conflict of interest.

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