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MINIREVIEWS

Current concepts in the management of non-cirrhotic non-malignant portal vein thrombosis

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Abstract

Non-cirrhotic non-malignant portal vein thrombosis (NCPVT) is an uncommon condition characterised by thrombosis of the portal vein, with or without extension into other mesenteric veins, in the absence of cirrhosis or intra-abdominal malignancy. Complications can include intestinal infarction, variceal bleeding and portal biliopathy. In this article, we address current concepts in the management of NCPVT including identification of risk factors, classification and treatment, and review the latest evidence on medical and interventional management options.

Key Words: Non-cirrhotic portal vein thrombosis; Portal vein; Mesenteric veins; Venous thrombosis; Portal hypertension

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Core Tip: The successful management of patients with non-cirrhotic non-malignant portal vein thrombosis (NCPVT) requires clinicians to diagnose and classify the condition correctly, meticulously identify underlying risk factors and select the appropriate treatment strategies based on the latest supporting evidence. Herein we provide a comprehensive review of current concepts in the management of NCPVT with suggested management algorithms.

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INTRODUCTION

Non-cirrhotic non-malignant portal vein thrombosis (NCPVT) refers to thrombosis of the portal vein and/or its intrahepatic branches in the absence of liver cirrhosis or intra-abdominal malignancy. The definition also encompasses those patients with thrombus extension into the splenic and/or superior mesenteric veins (SMV)[1]. Unlike portal vein thrombosis (PVT) in cirrhosis, NCPVT is an uncommon condition. Population prevalence estimates for portal vein thrombosis range from 0.05%-1% in autopsy studies[2,3]. More recent hospital series report standardised incidence rates between 0.7 per 100000 and 1.73-3.79 per 100000[4,5]. It should be noted however that in these studies approximately 30% of patients had cirrhosis and up to 44% of patients had solid organ malignancy.

Clinical features and diagnosis

Patients with NCPVT may present acutely with symptoms reflecting the consequences of recent thrombus formation, venous ischaemia and portal hypertension. The most common presenting symptoms are abdominal pain, fever and small volume ascites. Intestinal infarction, the most serious consequence of recent NCPVT with a mortality rate of up to 60%, is rare in patients treated promptly with anticoagulation[6]. On the other hand, NCPVT may be detected incidentally on imaging and patients with chronic NCPVT may present with complications from portal hypertension such as variceal bleeding or ascites. The distinction between recent and chronic NCPVT is critical as it has important implications for management strategies which will be discussed in detail later.

Diagnosis of NCPVT is based on imaging. The diagnostic performance of colour Doppler ultrasound and computed tomography (CT) portal angiography are similar with reported sensitivity and specificity ranging from 89%-93% and 92%-99% respectively[7,8]. Although not directly compared, sensitivity and specificity for magnetic resonance imaging (MRI) is higher at 100% and 98% respectively[9,10]. Cross-sectional imaging is required to exclude features of intestinal ischaemia, map thrombus extent and identify the presence and course of collateral vessels. It also facilitates assessment of underlying local risk factors such as pancreatitis or malignancy[11,12]. Recent thrombus typically appears as heterogenous material within the vessel lumen on ultrasound, with absence or reduction of flow on colour Doppler. CT features include non-contrast enhancing increased attenuation of the portal vein and MRI may show T2-hyperintense signal abnormality within the portal vein[13]. With chronicity, ultrasound may show areas of increased echogenicity reflecting calcification within the thrombus. Cross-sectional imaging may demonstrate the presence of multiple small porto-portal collaterals, termed cavernoma, and features of portal hypertension[13]. It is worth noting, however, that cavernoma is not synonymous with chronic portal vein thrombus since cavernous transformation of the portal vein has been observed to occur as early as 6-20 d post-initial thrombus formation[14]. Indeed, patients may have established cavernoma on imaging despite clinical and radiological features of recent thrombosis formation and should be managed as having recent thrombosis[15] (Figure 1).

Pathophysiological considerations

NCPVT results from factors influencing one or more features of Virchow's triad: Reduced portal blood flow, hypercoagulability, and vascular endothelial injury. Histologically recent thrombosis comprises a fibrin mesh with entrapped red cells and platelets. Over time this becomes organised with deposition of collagen and vascularisation of the clot[16].

In NCPVT portal hypertension arises due to obstruction of the portal vein lumen leading to increased resistance to flow creating back pressure within the portal system. Note that obstruction does not need to be complete to have significant haemodynamic consequences. This is because of Poiseuille's law, which states that flow is proportional to the vessel radius to the fourth power[1]. This mechanism of portal hypertension contrasts with that seen in cirrhosis where the increased portal pressures arise from a combination of increased intrahepatic resistance (creating back pressure) and increased portal inflow secondary to splanchnic vasodilation[17].

Two compensatory mechanisms have been postulated to maintain hepatic perfusion in the setting of portal vein obstruction. Firstly, a reflex increase in hepatic arterial flow and secondly rapid formation of porto-portal collaterals leading to cavernous transformation of the portal vein, as described above[18]. Where there is failure of recanalization of the occluded portal vein, the natural history is of cavernoma formation, obliteration of the native portal vein to form a fibrotic cord and, in some patients, the development of sequalae of portal hypertension[15].

CONCEPT 1 – IDENTIFICATION OF RISK FACTORS AND WORK-UP

Identification of risk factors

Risk factors for NCPVT can be classified as local or systemic (Table 1). Local factors such as trauma, surgery, and intra-abdominal inflammatory conditions, for example pancreatitis, are present in up to 35% of cases[1,19-21]. Systemic associations include myeloproliferative neoplasms (MPN), inherited or acquired thrombophilia, recent oral contraceptive use,

Table 1 Risk factors for non-cirrhotic non-malignant portal vein thrombosis, %

Risk factor	Prevalence	Investigations
Systemic		
Myeloproliferative neoplasm	21-32	JAK2 V617F mutation testing
		CALR mutation testing if platelets > 200 × 10^9/L and spleen ≥ 16 cm
		Consider bone marrow biopsy
Acquired thrombophilia		
Antiphospholipid syndrome	6	Lupus anticoagulant, anti-cardiolipin and anti-b2 glycoprotein-I antibodies (2 positive samples 12 wk apart)
Paroxysmal nocturnal haemoglobinuria	0.30	Flow cytometry (CD55 and CD59 deficient cells)
Inherited thrombophilia		
Prothrombin G20210A gene mutation	6-7	Prothrombin G20210A mutation testing
Factor V Leiden	3-7	Factor V Leiden mutation testing
Protein C deficiency	5-6	Protein C levels[1]
Protein S deficiency	3-5	Protein S levels[1]
Antithrombin deficiency	1-4	Antithrombin levels[1]
Hormonal (recent pregnancy/oral contraceptive)	16	Medical history
Other systemic disease *e.g.*, connective tissue disease, sarcoidosis, vasculitis, acute CMV infection	3	Variable
Obesity		Medical history
Local		
Abdominal trauma/surgery	14	Medical history/cross-sectional imaging
Inflammatory abdominal conditions *e.g.*, pancreatitis, biliary infection, appendicitis, inflammatory bowel disease	11	Variable
No cause identified	35-42	

[1]Interpret with caution in liver impairment.

Risk factors for non-cirrhotic non-malignant portal vein thrombosis[1,19]. CMV: Cytomegalovirus; CALR: Calreticulin.

obesity, paroxysmal nocturnal haemoglobinuria (PNH), acute cytomegalovirus (CMV) infection[22], and coronavirus disease 2019 infection[23]. MPN, including polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (MF) in order of frequency, are the most common systemic cause of NCPVT and are identified in up to 32% of patients[24]. Antiphospholipid syndrome is present in 6% of patients with NCPVT and the most common inherited thrombophilia, prothrombin (factor II) [1,19]. It is important to note that multiple thrombotic factors are identified in approximately 15% of patients. Ultimately in 35%-42% of patients no identifiable cause is found[1,19].

Diagnosis of MPN may be more challenging in patients with NCPVT since, in the presence of portal hypertension and hypersplenism, peripheral blood counts may be normal or even low. Testing for the JAK2V617F mutation, which is present in 95% of patients with PV and approximately 50% of patients with ET, is therefore useful. In a meta-analysis of 855 patients 86.6% patients with NCPVT and MPN were JAK2 positive. Moreover, JAK2 mutation analysis was positive in 15.4% patients without other features of MPN[24]. Mutations in calreticulin (CALR), the second most common mutation in ET and MF, are found in 0%-2% of patients with splanchnic thromboses and mutations in the thrombopoietin receptor gene (MPL) appear to be exceedingly rare[25]. In a large prospective cohort study, spleen height ≥ 16 cm and platelet count > 200 × 10^9/L had a 99% negative predictive value for the presence of CALR mutation in patients without JAK2 mutations[25]. This suggests that CALR mutation testing can be selectively applied to this group. Bone marrow biopsy, in conjunction with haematology consultation, should be considered in patients with unexplained NCPVT and negative work-up for MPN[19,26].

Current guidelines differ somewhat in recommendations for investigation of risk factors for NCPVT. European guidelines recommend a complete work-up for MPN, inherited and acquired thrombophilia in all patients, even in the presence of a clear local factor[26,27]. American guidelines, on the other hand, recommend investigation in those patients without a clear provoking factor and recommend against testing for inherited thrombophilia, as results rarely influence management and levels of protein C, S and antithrombin can be altered in the context of acute thrombosis[19,28].

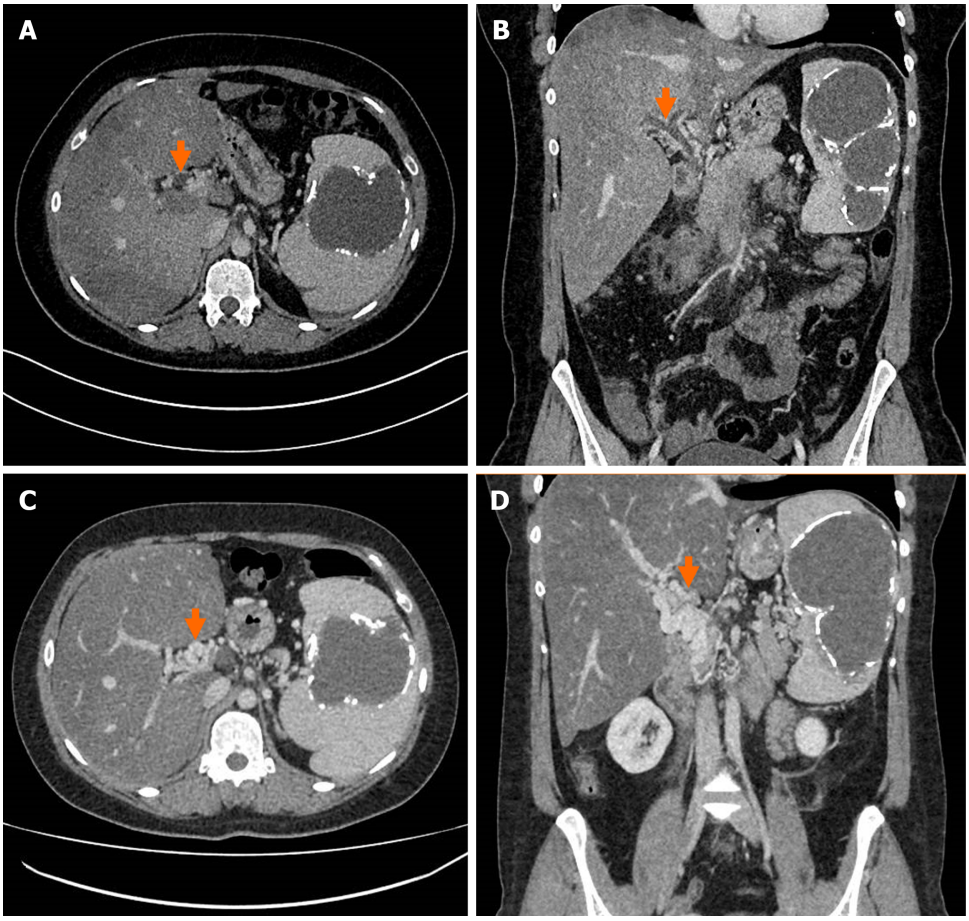

Figure 1 Cross-sectional images of recent portal vein thrombosis and subsequent cavernoma formation. A: Axial computed tomography demonstrating acute portal vein thrombosis (Orange arrow) with altered hepatic parenchymal attenuation secondary to ischaemia; there is an incidental large splenic cyst; B: Coronal computed tomography demonstrating acute portal vein thrombosis (Orange arrow) with altered hepatic parenchymal attenuation secondary to ischaemia; there is an incidental large splenic cyst; C: Axial computed tomography 6 months later in the same patient, demonstrating formation of portal vein cavernoma (Orange arrow); D: Coronal computed tomography 6 months later in the same patient, demonstrating formation of portal vein cavernoma (Orange arrow).

Exclusion of cirrhosis

It is important to exclude underlying cirrhosis because the natural history, work-up and management of patients with cirrhotic PVT differs from those with NCPVT[26]. For example, investigation for additional prothrombotic risk factors is not routinely recommended and whilst spontaneous recanalization is rare in NCPVT, it is more common in cirrhotic PVT [29].

The diagnosis of cirrhosis can be made on clinical, imaging, liver stiffness and histological evidence. It is important to note that some imaging features typically associated with cirrhosis, such as caudate lobe hypertrophy, may be seen in patients with NCPVT with cavernous transformation. However, hepatic nodules/nodular liver contour are not seen and features such as left lateral segment atrophy and a normal/enlarged segment IV are specific to NCPVT with cavernous transformation[30]. Liver stiffness is significantly higher in patients with cirrhosis than patients with NCPVT or porto-sinusoidal vascular disorder and liver stiffness measurement > 10 kPa, as determined by vibration controlled transient elastography should prompt consideration of underlying advanced chronic liver disease[26,31]. In case of uncertainty a liver biopsy is indicated.

CONCEPT 2 - CLASSIFICATION

Classification of NCPVT is important both to inform clinical decision making and to provide standardised definitions for research. NCPVT can be classified based on temporal characteristics (recent, chronic, change over time), anatomical characteristics (location of thrombus within the portal vein and its branches, extension of thrombus into splenic and SMV, degree of luminal occlusion, presence of collateralisation), and functional consequences (presence of symptoms, gut ischaemia and portal hypertensive complications).

Various classification systems of portal vein thrombus have been proposed, which have been summarised in recent The American association for study on liver diseases (AASLD) guidelines[19,32]. It is important to note that none of these are specific to NCPVT; in fact, the majority have been developed based on data limited to liver transplant patients and not all correlate with clinically meaningful outcomes. To standardise clinical and research reporting, AASLD and Baveno VII

have recently proposed standardised nomenclature for portal vein thrombus description (cirrhotic and non-cirrhotic) based on time course, percent occlusion of the main portal vein, and response to treatment of interval change (Table 2)[19,26]. Of note, extension of thrombus into other mesenteric veins, which has been associated with worse outcomes, is not included in this classification system[6,12,33,34].

Time course

Portal vein thrombus is defined as recent when it is presumed to have occurred within the past 6 months. The term recent is preferred to the term acute as the latter implies the presence of symptoms, yet not all patients with recent portal vein thrombus are symptomatic. Portal vein thrombus which persists beyond 6 months is labelled chronic[19]. The clinical relevance of this definition is supported by data from a large prospective multicentre cohort study of patients with NCPVT which showed recanalization with anticoagulant treatment was only achieved in those patients with a thrombus duration of less than 6 months[6].

Degree of luminal occlusion

Portal vein thrombus is considered completely occlusive when there is no luminal flow. Partially occlusive thrombus is defined as occupying > 50% of the vessel lumen and minimally occlusive < 50% of the vessel lumen. Intuitively, higher grades of occlusion should be associated with a greater risk of complication. Indeed, in cirrhotic patients undergoing liver transplantation, 30-d and 1-year mortality rates are significantly higher for those with complete occlusion than those with partial occlusion[35]. On the other hand, in a cohort of 60 patients, 60% of whom had NCPVT, there was no difference in portal hypertensive complications between patients with complete or incomplete luminal occlusion, despite a significantly higher prevalence of cavernous transformation in patients with complete luminal occlusion[34].

Extent of thrombus

Multiple studies demonstrate the relevance of extension of portal vein thrombus into other mesenteric vessels, particularly the SMV. Patients with extensive thrombus are more likely to be symptomatic[34,36], less likely to achieve portal vein recanalization with anticoagulation[6,37], and have higher rates of intestinal infarction particularly when there is involvement of the second order radicles of the SMV[12,36].

CONCEPT 3 – TREATMENT TARGETS AND ANTICOAGULATION

The goals of treatment differ between patients with recent and chronic NCPVT. In patients with recent thrombus the primary aim is to prevent thrombus extension and mesenteric infarction[19]. Complete recanalization is perhaps the ultimate goal, however it is not achieved in the majority despite anticoagulation[6]. In patients with chronic NCPVT the goals of treatment are to prevent recurrent thrombus and manage the sequelae of portal hypertension. Figures 2 and 3 provide suggested management algorithms for recent and chronic NCPVT.

Anticoagulation for recent NCPVT

At present, systemic anticoagulation is the treatment of choice for patients presenting with recent NCPVT with supporting data from several observational studies. Initial anticoagulation with low molecular weight heparin (LMWH) is preferred over unfractionated heparin due to higher rates of heparin-induced thrombocytopaenia with the latter[26]. Complete portal vein recanalization occurs in approximately 40% of patients treated with prompt anticoagulation and mesenteric infarction is uncommon[6,37-40]. In contrast, spontaneous recanalization appears to be rare, with no untreated patients achieving recanalization in two retrospective studies[37,38].

Reported risk factors for failure to recanalize include the presence of ascites at diagnosis, splenic vein involvement[6], delay in initiation of anticoagulation beyond 1 week after diagnosis, and the presence of multiple prothrombotic conditions[38]. Extensive thrombus has been identified as a risk factor for failure of complete recanalization[37] and for intestinal resection[12], although a conflicting study found no correlation between extent of thrombus and recanalization rate[38]. Type 2 diabetes appears to be an additional independent risk factor for intestinal resection[12].

A large prospective observational study demonstrated that maximal recanalization of the main portal vein is achieved within 6 months and that further anticoagulation beyond this point did not achieve higher rates of recanalization. By contrast there did not seem to be a plateau for SMV or splenic vein recanalization with patency rates of 61% and 54% respectively at 1 year and at 73% and 80% respectively at the end of follow-up[6]. Notably, in this study the degree of luminal obstruction (partial or complete) was not specified, which may explain the apparent difference in recanalization rates between different segments of the splanchnic veins[41]. Current guidelines recommend anticoagulation is commenced at the earliest opportunity irrespective of signs of intestinal ischaemia and continued for at least 6 months with prolonged anticoagulation in those patients with risk factors for recurrence[26].

Most studies have reported low rates of major bleeding in patients treated with anticoagulation for recent NCPVT. Two studies report no significant difference in gastrointestinal bleeding rates between patients treated with anticoagulation and those who were not, whilst a third single centre study showed a 2-fold increased risk of bleeding with anticoagulation[38,39,42]. Anticoagulation was not associated with increased severity of bleeding or mortality[42]. A recent large meta-analysis of anticoagulation for splanchnic venous thrombosis, including patients with recent and chronic NCPVT, showed that anticoagulation was associated with lower rates of major bleeding and overall mortality[43].

Table 2 Recommended standardized nomenclature for portal vein thrombosis description

Feature	Definition
Time course	
Recent	Portal vein thrombus presumed to be present for < 6 months
Chronic	Portal vein thrombus present or persistent for > 6 months
Percentage occlusion of main portal vein	
Completely occlusive	No persistent lumen
Partially occlusive	Clot obstructing > 50% of original vessel lumen
Minimally occlusive	Clot obstructing < 50% of original vessel lumen
Cavernous transformation	Gross porto-portal collaterals without original portal vein seen
Response to treatment or interval change	
Progressive	Thrombus increases in size or progresses to more complete occlusion
Stable	No appreciable change in size or occlusion
Regressive	Thrombus decreases in size or degree of occlusion

Recommended standardized nomenclature for portal vein thrombosis description[26].

Anticoagulation for chronic NCPVT

The aim of anticoagulation in patients with chronic NCPVT is to prevent recurrence of thrombus formation. The data supporting this practice is mixed with two early retrospective studies showing no difference in overall recurrence rates between anticoagulated and non-anticoagulated patients[39,42]. However, when patients were stratified according to the presence of an underlying prothrombotic state, there was a significantly lower rate of recurrent portal venous thrombosis during periods of anticoagulation compared to periods without anticoagulation (0.82 *vs* 5.2 per 100 patient years, P = 0.01)[39]. A subsequent large multicentre prospective cohort study of 604 patients with splanchnic vein thrombus confirmed that anticoagulation was negatively correlated with the risk of recurrent thrombosis [hazard ratio (HR) 0.89] and was not significantly associated with risk of major bleeding[44]. A small single centre retrospective study also showed an association between anticoagulation and reduced risk of mortality in patients with chronic portomesenteric and portosplenomesenteric thrombus[45].

More recently a landmark randomized controlled trial of rivaroxaban versus no anticoagulation in 111 patients with chronic NCPVT (or recent NCPVT diagnosed over 6 months before trial entry), but without major risk factors for recurrence, was stopped early due to high rates of recurrent thrombosis in the non-treated arm (19.7 *vs* 0 per 100 person-years, P = 0.0008)[46]. Following a second phase, where all patients were offered anticoagulation, re-thrombosis rates remained high in those who declined it (16.0 *vs* 0.4 per 100 person-years). As in earlier studies there was no significant difference in rates of major bleeding between anticoagulated and non-anticoagulated patients, although incidence of minor bleeding was increased nearly 5-fold. High rates of recurrent thrombosis in patients with chronic NCPVT, without known pro-thrombotic conditions and not receiving anticoagulation, were also observed in a recent multicentre cohort study with 27% patients experiencing recurrent thrombus at a median of 18 months[47]. Of note, more than 50% of patients experiencing recurrent splanchnic thrombosis were asymptomatic, highlighting the importance of surveillance imaging in this group.

Taken together the data support long-term anticoagulation for patients with chronic NCPVT where there are significant risk factors for recurrence or a prior history of intestinal infarction. Major risk factors include MPN, solid organ malignancy, antiphospholipid syndrome, PNH, homozygous or compound heterozygous factor V Leiden or prothrombin G20210A gene mutations, and a personal or first-degree familial history of unprovoked deep vein thrombosis[46]. Although more studies are required, there is also growing evidence of high rates of recurrent thrombosis in patients without apparent risk factors and benefit of anticoagulation in this group.

Risk factors for recurrence

Several studies have identified that the presence of a prothrombotic disorder (MPN, inherited or acquired thrombophilia) is associated with an increased risk of thrombotic recurrence in patients with NCPVT with hazard ratios ranging from 3.1-9.0[39,42,44]. In a large prospective cohort study independent risk factors associated with recurrent thrombosis were unprovoked splanchnic vein thrombus (HR 3.8), male sex (HR 4.7), solid cancer (HR 6.2), and MPN (HR 9.0)[44]. It should be noted that most papers reporting on NCPVT excluded patients with known solid organ malignancy.

In a post-hoc analysis of data from the randomized controlled trial of rivaroxaban in patients with NCPVT without major risk factors for recurrent thrombosis, the authors identified that D-dimer ≥ 500 ng/mL at 1 month following discontinuation of anticoagulation was associated with an increased risk of recurrent thrombosis (HR 7.78) with a negative predictive value of 93.8%[46]. In contrast, D-dimer ≥ 500 ng/mL was not found to be predictive or recurrent thrombus in a recent multicentre retrospective cohort, whereas Factor VIII levels ≥ 150% were (HR 7.1)[47]. Further validation of this

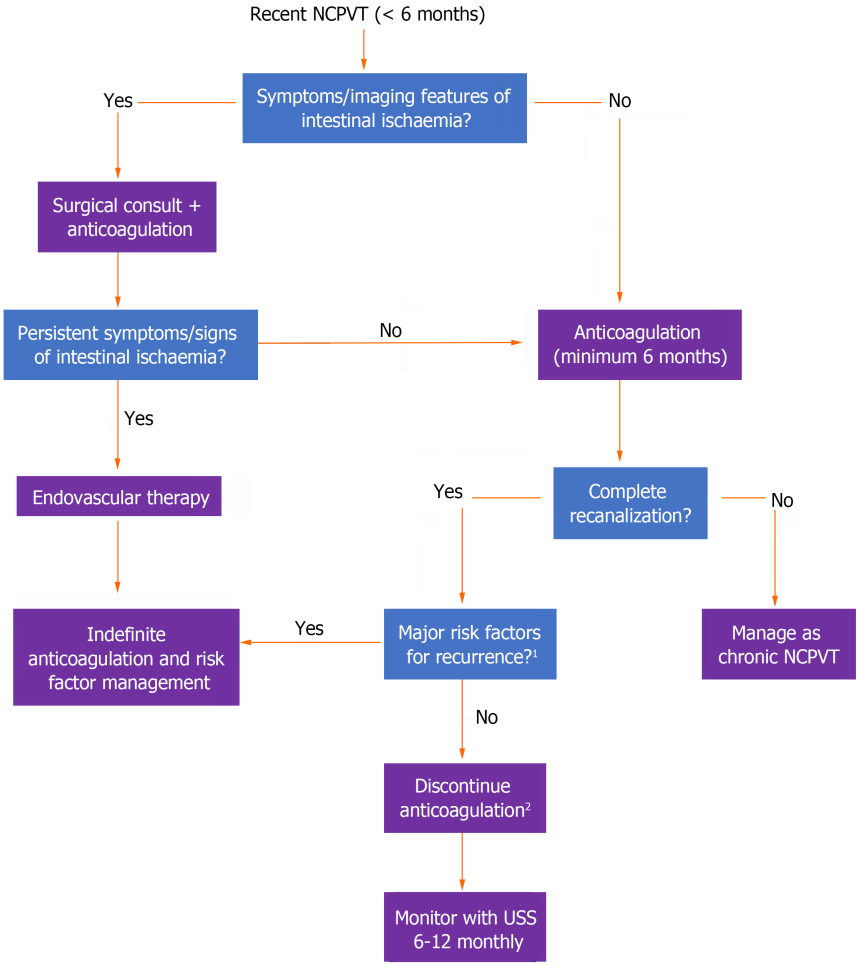

Figure 2 Suggested management algorithm for recent non-cirrhotic non-malignant portal vein thrombosis. [1]Major risk factors include: Myeloproliferative neoplasms, antiphospholipid syndrome, paroxysmal nocturnal haemoglobinuria, homozygous or compound heterozygous factor V Leiden or prothrombin G20210A gene mutations, personal or first-degree familial history of unprovoked deep vein thrombosis. [2]Consider measuring D-dimer. If D-dimer > 500 ng/mL at 1 month following anticoagulation discontinuation consider long-term anticoagulation. NCPVT: Non-cirrhotic non-malignant portal vein thrombosis.

finding in a prospective study is required.

Next generation sequencing may prove a useful tool in stratifying the risk of recurrent thrombosis amongst patients with apparent idiopathic or local-factor only NCPVT. In a study including 71 patients with idiopathic/local-factor only NCPVT, next generation sequencing identified high molecular risk variants (mutations in genes implicated in myeloid clonal pathology other than JAK2, CALR and MPL) were identified in 38% of patients. Cumulative incidence of recurrent thrombosis was significantly higher in patients with high molecular risk variants than in those without[48].

Choice of oral anticoagulant

Vitamin K antagonists (VKA) have traditionally been the mainstay of oral anticoagulation for patients with NCPVT. Compared with VKA, direct oral anticoagulants (DOAC) offer convenient advantages of fixed dosing without monitoring requirements and fewer drug-drug interactions which make them an appealing option for oral anticoagulation. To date however there are no randomized controlled trials comparing DOAC to VKA in patients with NCPVT. A recent single-arm prospective study of rivaroxaban in 103 patients with symptomatic recent splanchnic vein thrombus showed similar outcomes to existing studies with 47.3% of patients achieving complete recanalization at 3 months and major bleeding rates of 2.1%[40]. Rivaroxaban also appeared safe and effective in the prevention of recurrent NCPVT in patients without major risk factors for recurrence[46].

A meta-analysis of 3 retrospective cohort studies, including 459 patients with NCPVT, reported significantly higher rates of recanalization with DOAC compared to VKA (OR 4.33, 95%CI 2.4-7.83) and lower risks of bleeding compared to no treatment (OR 0.09, 95%CI 0.03-0.29), LMWH (OR 0.13, 95%CI 0.03-0.62) or VKA (OR 0.12, 95%CI 0.02-0.69). Notably, there was no statistically significant difference in recanalization rates between DOAC and no treatment, or DOAC and LMWH[49]. Overall the GRADE certainty of evidence was rated as low to very low due to the quality of the included studies. Of note, DOAC should be avoided in patients with triple positive antiphospholipid syndrome as they are inferior to VKA in preventing recurrent (particularly arterial) thrombosis[50].

In patients with inflammatory bowel disease associated NCPVT a retrospective cohort study showed higher rates of complete radiographic resolution (96% *vs* 55%, $P = 0.0006$) and shorter time to resolution (3.9 *vs* 8.5 months, $P = 0.02$) in patients treated with DOAC compared to warfarin[51]. Similarly in patients with a provoked, post-surgical portal vein

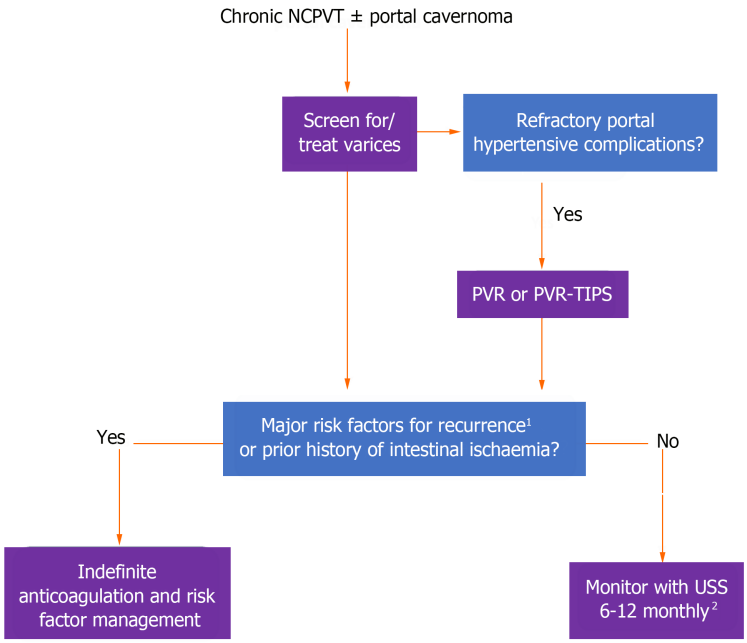

Figure 3 Suggested management algorithm for chronic non-cirrhotic non-malignant portal vein thrombosis. [1]Major risk factors include: Myeloproliferative neoplasms, antiphospholipid syndrome, paroxysmal nocturnal haemoglobinuria, homozygous or compound heterozygous factor V Leiden or prothrombin G20210A gene mutations, personal or first-degree familial history of unprovoked deep vein thrombosis. [2]Consider long-term anticoagulation on a case-by-case basis. Where a decision is made to discontinue existing anticoagulation consider measuring D-dimer. If D-dimer > 500 ng/mL at 1 month following anticoagulation discontinuation consider long-term anticoagulation. NCPVT: Non-cirrhotic non-malignant portal vein thrombosis; PVR: Portal vein recanalization; TIPS: Transjugular intrahepatic portosystemic shunt.

thrombosis, DOAC were superior to enoxaparin, warfarin and no treatment for complete radiographic resolution at 1 year[52].

LMWH has been the treatment of choice for cancer-associated venous thrombosis due to the lower risk of recurrent thrombosis compared to VKA. More recent data show no significant difference in rates of thrombosis recurrence or major bleeding in patients treated with DOAC for cancer-associated venous thrombosis compared to VKA, although caution is recommended in patients at high risk of bleeding[53]. The risk of bleeding in patients with cancer-associated splanchnic vein thrombosis does not appear to be different to patients with cancer-associated venous thromboses at other sites[54]. However, the risk of gastrointestinal bleeding is higher with DOAC than LMWH in patients with gastrointestinal tract malignancy[55] and guidelines recommend caution in this situation[56,57]. In addition, drug-drug interactions with chemotherapeutic agents may influence the choice of anticoagulant.

In pregnant patients LMWH is recommended as the anticoagulant of choice during pregnancy. VKA or LMWH are recommended in breastfeeding patients and DOAC should be avoided[58]. As it shows in Table 3 for a summary of commonly used anticoagulants.

CONCEPT 4 - ENDOVASCULAR THERAPY AND SURGERY

Endovascular therapy is proposed as rescue therapy in patients with recent NCPVT and failure of response to anticoagulation with ongoing intestinal ischaemia, and in patients with chronic NCPVT and refractory complications of portal hypertension[59]. Techniques include catheter-directed local thrombolysis, mechanical thrombectomy, transjugular intrahepatic portosystemic shunt (TIPS) insertion and portal vein recanalization (PVR) with or without TIPS.

Endovascular therapy for recent NCPVT

Early studies of catheter-directed local thrombolysis for patients with recent portal vein thrombosis reported high rates of complications including major bleeding in 50%-60% patients[60,61]. More recent studies report favourable outcomes with high rates of recanalization and lower rates of major complications[1,59,62-65].

A retrospective series of 35 patients with recent NCPVT and persistent abdominal pain despite anticoagulation reported a stepwise treatment protocol of low-dose systemic alteplase followed by clot dissolution therapy (local tissue plasm activator and mechanical/aspiration thrombectomy) plus TIPS if required. 49% received clot dissolution therapy and TIPS was inserted in 43%. Overall symptom resolution was achieved in 88% with a degree of recanalization in 69% which persisted in 60% at a median follow-up of 11 months. However, 9 (26%) patients required intestinal resection and 1 (3%) patient suffered intracranial haemorrhage[62,63].

Recanalization rates of 100% were reported in a retrospective study of 32 patients with recent NCPVT who underwent TIPS and mechanical thrombectomy either for persistent abdominal pain/intestinal ischaemia or portal hypertensive

Table 3 Comparison of commonly used anticoagulants

Considerations	Anticoagulant					
	Low molecular weight heparin	Vitamin K antagonist	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Standard dose	Parenteral. Weight-based dosing	Dosed according to INR. Usual target 2-3	10 mg daily for 7 d then 5 mg twice daily	150 mg twice daily after 5 d parenteral antico-agulant	60 mg once daily after 5 d parenteral antico-agulant	15 mg twice daily for 21 d then 20 mg once daily
Age	-	-	-	75-79 years reduce dose to 110-150 mg twice daily. ≥ 80 years reduce dose to 110 mg twice daily	-	-
Weight	Weight-based dosing	-	-	-	< 61 kg reduce dose to 30 mg once daily	-
Renal impairment	Use with caution if CrCl < 30 mL/min. Avoid enoxaparin if CrCl < 15 mL/min	-	Avoid if CrCl < 15 mL/min. Use with caution if CrCl 15-29 mL/min	Avoid if CrCl < 30 mL/min. Consider dose reduction to 110-150 mg twice daily if CrCl 30-50 mL/min	Avoid if CrCl < 15 mL/min. Reduce dose to 30 mg once daily if CrCl 15-50 mL/min	Avoid if CrCl < 15 mL/min. Consider dose reduction to 15 mg daily if CrCl 15-49 mL/min
Pregnancy	Safe	Avoid (especially 1st/ 3rd trimester)	Avoid	Avoid	Avoid	Avoid
Breastfeeding	Safe	Safe	Avoid	Avoid	Avoid	Avoid
Reversal agent	Protamine sulphate (partially effective)	Vitamin K, prothrombin complex concentrate	Andexanet alfa	Idarucizumab	None	Andexanet alfa
Other		Multiple drug and food interactions	DOAC contraindicated in anti-phospholipid syndrome			

Comparison of commonly used anticoagulants[84]. DOAC: Direct oral anticoagulants.

complications. Intention to treat primary TIPS patency was maintained in 78% at 1 year. One (3%) patient experienced hepatic encephalopathy and 3 (9%) had return of symptoms at 1 year[64].

A non-randomized prospective observational study of 65 patients compared medical treatment with initial endovascular treatment (mechanical thrombectomy followed by local thrombolysis +/- stent insertion) and showed higher rates of complete recanalization with endovascular treatment (54% *vs* 30%, $P < 0.001$). There was no difference in the rates of intestinal infarction requiring surgery, however major bleeding was more common in the endovascular group (5% *vs* 0%). Length of hospitalisation and duration of intensive care unit intensive care stay were both shorter in the medical group. It is notable that the recanalization rate in the medical group is lower than reported in other studies[66].

Endovascular therapy for chronic NCPVT

For patients with chronic portal vein thrombosis and refractory portal hypertensive complications despite medical and endoscopic management, PVR with or without TIPS has been shown to be effective in restoring portal vein patency. A meta-analysis of mostly cirrhotic patients with chronic PVT showed TIPS was feasible in 95% with a 10% major complication rate, achieving 12-month portal vein patency of 79%[67]. Most patients did not have cavernous transformation, which makes TIPS more challenging.

For patients with portal cavernoma PVR-TIPS *via* percutaneous transhepatic or trans-splenic provides a treatment option, with recanalization rates from 73.3%-100% and re-thrombosis rates of 0%-33%. Percutaneous access has a higher rate of bleeding compared to TIPS and may require embolization of the access tract[59]. In the largest study to date, 39 patients with NCPVT and portal cavernoma underwent PVR-TIPS with 48.7% *via* the trans-splenic approach. Primary TIPS patency was 63% at 36 months and secondary patency 81%. Notably 31% patients experienced TIPS thrombosis, 3 patients (7.7%) hepatic encephalopathy and 1 patient heart failure (2.6%)[68]. For patients in whom recanalization of the main portal vein is not possible, TIPS *via* a large collateral cavernoma vessel (transcollateral TIPS) can be effective with similar rates of rebleeding and shunt dysfunction and lower rates of overt hepatic encephalopathy[69].

Whether TIPS is required in patients with NCPVT, who have pre-sinusoidal hypertension and normal intrahepatic resistance, is a matter of debate. The presence of TIPS simplifies access for repeat intervention in the case of recurrent thrombus but carries short term risk as described above, and the long-term consequences in patients without cirrhosis are not known. A recently reported retrospective study of 31 patients with chronic NCPVT and portal cavernoma assessed the performance of PVR and covered stent placement without TIPS, with the most frequent indications being gastrointestinal bleeding or symptomatic PVT with abdominal pain. Technical success was achieved in 87%, with 78%

primary patency and 78% patients free of portal hypertensive complications at 5 years. Risk factors for failure of PVR alone included extension of thrombus into the intrahepatic portal veins and abdominal pain as the indication for treatment, with the authors proposing combined PVR-TIPS in these patients[70]. Furthermore, the largest series comparing PVR and stent placement (PVS) with PVR-TIPS, in 54 patients with NCPVT and cavernoma, showed significantly lower rates of stent occlusion, recurrent variceal bleeding and serious adverse events in the PVS group[71].

In the current studies, long-term anticoagulation was continued in most patients after PVR ± TIPS placement. Further prospective studies are required before a firm recommendation for ongoing anticoagulation can be made.

Surgery

Although surgery, in the form of Meso-Rex bypass, is the treatment of choice for chronic NCPVT in the paediatric population, since it restores physiological portal venous flow, it is rarely performed in adults[1]. A case series of 14 adults who underwent the procedure for recurrent GI bleeding, sepsis from portal biliopathy and/or severe abdominal pain reported symptomatic relief in 87.5% of patients and shunt patency of 64.3% at last follow-up. There were however high rates of major complications (35.7%) including one death (7%)[72].

CONCEPT 5 – MANAGEMENT OF PORTAL HYPERTENSIVE COMPLICATIONS

Patients with NCPVT may develop complications of portal hypertension including variceal bleeding, ascites, encephalopathy and portal biliopathy. In patients with chronic NCPVT the risk of developing varices has been reported as 2% at 1 year and 22% at 3 years. The risk of bleeding in patients with high-risk varices on primary prophylaxis is approximately 9%, 20% and 32% at 1, 3 and 5 years respectively. There does not appear to be a difference in efficacy between non-selective beta blockers (NSBB) and endoscopic variceal ligation (EVL) although no comparative trials have been reported[[1,73]. Consequently, current guidelines recommend screening for varices in patients with NCPVT who do not achieve recanalization within 6 months and treating high risk varices with either NSBB or EVL. For secondary prophylaxis a combination of NSBB and EVL is recommended, as per patients with cirrhotic portal hypertension[19,26,28]. Theoretically, unlike in patients with cirrhosis, carvedilol may not provide additional benefit over propranolol or nadolol since intrahepatic resistance is not increased in most patients with NCPVT. As discussed previously, PVR with or without TIPS is an option for patients with recurrent portal hypertensive bleeding despite adequate medical/endoscopic prophylaxis. Ascites and hepatic encephalopathy appear to be less common than in patients with cirrhosis but their management is the same[59].

Portal biliopathy

Portal biliopathy, also termed portal cavernoma cholangiopathy, refers to biliary abnormalities occurring patients with chronic NCPVT. These changes occur secondary to extrinsic biliary compression from portal cavernoma and/or ischaemic cholangiopathy due to alterations in portal blood flow. Incidental biliary abnormalities are very common imaging findings in patients with portal cavernoma, however approximately 5%-38% of patients have symptoms such as jaundice, abdominal pain or cholangitis[74,75]. Only symptomatic patients require treatment which may involve both biliary and portal decompression[76]. It is important to note the potential increased risk of bleeding from pericholedochal varices in patients undergoing ERCP and sphincterotomy. The role of medical therapy with ursodeoxycholic acid has not been evaluated in any large studies and at present is unproven[77].

CONCEPT 6 – MANAGEMENT OF UNDERLYING PROTHROMBOTIC DISORDERS

All patients with underlying prothrombotic conditions should be managed in conjunction with a haematologist. Evidence that treatment of underling MPN impacts on the risk of NCVPT recurrence is however limited. Three large cohort studies did not show any difference in recurrence rates between patients receiving cytoreductive treatment and those who did not[78-80]. Interestingly, in a large cohort including patients with MPN and thrombosis at any site, cytoreductive therapy was associated with a reduction in risk of deep vein thrombosis and pulmonary embolus but not PVT[79]. On the other hand, a systematic review of 10 observational studies including 738 patients with MPN and a prior history of VTE (39% with prior splanchnic vein thrombus), reported lower rates of recurrent VTE in patients treated with both antithrombotic and cytoreductive therapy than with either therapy alone. There was no subgroup analysis of MPN-SVT patients only and limited data on recurrent thrombosis type[81]. Ruxolitinib, a JAK1/2 inhibitor, is effective in reducing spleen size and symptom burden in patients with MPN-associated splanchnic vein thrombus with no effect on thrombus extension[82].

In patients with splanchnic thrombosis secondary to paroxysmal nocturnal haemoglobinuria, treatment with eculizumab is associated with a significant reduction in recurrent venous thrombosis events (2.6 *vs* 14.2 per 100 patient-years) and reduced mortality (2.6 *vs* 8.7 per 100-patient years)[83].

CONCLUSION

Non-cirrhotic portal vein thrombosis (NCPVT) is an uncommon condition characterised by thrombosis of the portal vein, with or without extension into other mesenteric veins, in the absence of cirrhosis. Optimal management of this condition

requires thorough evaluation of both local and systemic risk factors, of which MPNs are the most common, and correct classification according to time course, degree of luminal occlusion, and extent of thrombus. Prompt treatment of recent NCPVT with anticoagulation is mandatory and results in low rates of intestinal infarction. For patients with persistent symptoms despite anticoagulation, endovascular therapies including catheter directed thrombolysis, mechanical thrombectomy and TIPS, have high success rates in achieving recanalization. Patients with chronic NCPVT are at risk of portal hypertensive complications and recurrent thrombosis. Recommendations for surveillance and management of complications parallel those for patients with cirrhosis. Long-term anticoagulation is recommended for patients with risk factors for recurrent thrombosis, though recent data suggests that risk of recurrent thrombosis is high even in patients without overt risk factors for recurrence. DOAC are effective in preventing re-thrombosis and in retrospective studies perform better than VKA. Patients with pro-thrombotic conditions should be managed in conjunction with a haematologist, though evidence that cytoreductive therapy reduces re-thrombosis is scant. Percutaneous PVR, with or without TIPS, is maturing as an interventional technique to manage patients with chronic NCPVT and refractory portal hypertensive complications. These patients must be managed by a multidisciplinary team with appropriate expertise due to the high rate of complications. Further research is required to determine whether all patients with chronic NCPVT would benefit from anticoagulation, the role of advanced diagnostics including next generation sequencing in identifying patients at risk of re-thrombosis, and whether TIPS provides additional benefit to PVR techniques.

FOOTNOTES

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