

Vascular liver disorders (II): portal vein thrombosis

J. Hoekstra, H.L.A. Janssen*

Department of Gastroenterology and Hepatology (room Ha 206), Erasmus MC, University Medical Center Rotterdam, Postbus 2040, 3000 CA Rotterdam, the Netherlands, *corresponding author: tel.: +31 (0)10-703 59 42, fax: +31 (0)10-436 59 16, e-mail: h.janssen@erasmusmc.nl

ABSTRACT

Portal vein thrombosis (PVT) is a rare disorder that is associated with a variety of underlying conditions, of which liver cirrhosis, malignancy and myeloproliferative disorders are the most common. Based on clinical presentation and results of imaging, two different entities can be identified, acute and chronic PVT. Anticoagulation therapy is recommended for all patients with acute PVT in an attempt to prevent further thrombosis and to promote recanalisation of the obstructed veins. Chronic PVT is characterised by the presence of a portal cavernoma and development of portal hypertension. Bleeding from ruptured oesophageal or gastric varices is the main complication of portal hypertension in these patients. Both endoscopic therapy and β -adrenergic blockade are used for the prevention and treatment of gastrointestinal bleeding. In the absence of bleeding, continuous anticoagulant therapy should be considered for the group of chronic PVT patients in whom an underlying prothrombotic factor can be identified. With adequate management of complications and concurrent diseases, prognosis of PVT is good in patients without underlying cirrhosis or malignancies.

KEYWORDS

Anticoagulation, myeloproliferative disorder, portal hypertension, portal vein, thrombosis

INTRODUCTION

The portal vein forms the backbone of the portal venous system that allows for blood from the digestive organs to flow towards the liver. Thrombosis of the portal vein can occur both in children and adults and results in significant

haemodynamic changes.¹ As with other forms of venous thrombosis, portal vein thrombosis (PVT) is associated with a number of different precipitating factors, both inherited and acquired.²⁻⁵ Though it is considered a rare disorder, a recent autopsy study showed the life-time risk of PVT in the general population to be 1%.⁶ In adults, clinical presentation is highly variable but depending on the duration of symptoms and results of imaging, PVT can usually be classified as either acute or chronic.⁷ In the past decade a number of, mainly retrospective, studies have been performed in patients with PVT. Results from these studies have significantly contributed to the current understanding of this vascular liver disorder. However, many questions remain unanswered and there is still much debate concerning the optimal treatment strategy for both acute and chronic PVT. In this review we will discuss the aetiology and clinical characteristics of PVT, with special attention for the management of this disorder.

AETIOLOGY

Both local (hepatobiliary) and systemic (thrombophilic) risk factors have been associated with thrombosis of the portal vein (table 1).^{2,8-10} In children, infectious causes of PVT, such as sepsis or omphalitis, are frequently present. Specifically in neonates, catheterisation of the umbilical vein is an important risk factor for development of PVT.^{11,12} In the adult population, liver cirrhosis and hepatobiliary malignancies are the most common local precipitating factors that together account for a large proportion of cases of PVT.⁶ In patients with liver cirrhosis, the reported incidence of PVT varies from 6 to 17%.¹³⁻¹⁵ Patients with more advanced stages of cirrhosis have a higher risk of PVT than patients with compensated liver disease.¹⁶ Development of thrombosis in cirrhotic patients is thought to be caused by both reduced portal blood flow

Table 1. Risk factors for the development of portal vein thrombosis

Local (hepatobiliary) factors	Systemic (thrombophilic) factors
Liver cirrhosis	Inherited:
(Hepatobiliary) malignancy	• Factor V Leiden mutation
Intra-abdominal infection/inflammation:	• Factor II (prothrombin) mutation
• Pancreatitis	• Protein C deficiency
• Cholecystitis	• Protein S deficiency
• Diverticulitis	• Antithrombin deficiency
• Appendicitis	Acquired:
• Inflammatory bowel disease	• Myeloproliferative disorder
• Omphalitis	• Antiphospholipid syndrome
Iatrogenous injury of the portal vein:	• Paroxysmal nocturnal hemoglobinuria
• Splenectomy	• Oral contraceptives
• Abdominal surgery	• Pregnancy or puerperium
• Umbilical vein catheterisation	• Hyperhomocysteinemia
	• Malignancy

and the effects of periportal fibrosis. Thrombus formation in patients with a local malignancy is usually related to direct compression or invasion of the portal vein by tumour mass. The incidence of PVT in patients with hepatocellular carcinoma (HCC) is 10 to 44%¹⁷⁻¹⁹ and appears to increase even further when concurrent cirrhosis is present.⁶ For this reason, diagnosis of PVT in a patient with liver cirrhosis should raise awareness for the presence of HCC. Other known local risk factors, such as pancreatitis, abdominal surgery and inflammatory bowel disease, are associated with a lower risk of PVT and are only encountered in a minority of patients.^{3,20,21} In contrast, it is now clear that in many patients with noncirrhotic nonmalignant PVT, a systemic, thrombophilic risk factor is present. Over the past two decades, a number of systemic conditions, either inherited or acquired, that result in a thrombogenic phenotype have been identified as risk factors for the development of PVT.^{2,8,9,22} Of these factors, myeloproliferative disorders (i.e. polycythaemia vera, essential thrombocythaemia and myelofibrosis) are by far the most common. In a recent study, a myeloproliferative disorder (MPD) was found in 37% of patients with noncirrhotic nonmalignant PVT.²³ Less frequent systemic risk factors associated with PVT are factor V Leiden mutation, prothrombin gene mutation and inherited deficiencies of protein C, protein S and antithrombin.^{2,8} Moreover, in concordance with venous thrombosis at other sites, the aetiology of PVT is often multifactorial, as in many patients a combination of underlying risk factors can be identified.²⁴ This was not only demonstrated in patients with noncirrhotic nonmalignant PVT,^{2,23} but also in cirrhotic patients with PVT.²⁵ In a cohort of patients with liver cirrhosis and PVT, a concurrent systemic risk factor was present in 70% of patients.^{26,27} Furthermore, patients with PVT also seem to be at an increased risk of developing other venous thromboembolic events.^{28,29}

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Acute PVT

An acute obstruction of the portal vein usually manifests itself as a sudden onset of abdominal pain, which may be very severe. Other symptoms that can occur are nausea, fever and diarrhoea.³ Whereas in the past, very few patients were diagnosed with acute PVT, due to increased awareness and improved imaging this disease entity is increasingly being recognised.³⁰ On physical examination the majority of patients will exhibit splenomegaly, but ascites is usually absent. Laboratory investigations provide few clues and unless an underlying liver disease is present liver function tests are usually (near) normal. However, using noninvasive imaging techniques the diagnosis of PVT can easily be established. Doppler ultrasound, computerised tomography (CT) or magnetic resonance imaging (MRI) can all be applied to demonstrate either the absence of flow or the presence of a thrombus in the portal vein (*figure 1*).³¹⁻³³ Additionally, with these imaging modalities it is possible to visualise the extent of the thrombosis. If apart from the portal vein, the mesenteric veins are also obstructed, there is a substantial risk of intestinal ischaemia and subsequent bowel infarction.³⁴ This is the most severe complication of acute portal vein thrombosis and often requires immediate surgical intervention. Fortunately, intestinal infarction occurs very infrequently; in a recent study less than 5% of patients with acute PVT suffered from this complication.³⁵ Once PVT is diagnosed, patients should be screened for underlying aetiological factors. Identification of a single

Figure 1. Computed tomography image of the liver (L) of a patient with portal vein thrombosis showing the presence of thrombotic material (arrow) in the lumen of the portal vein (PV)



risk factor does not diminish the need for a further search because multiple risk factors may be present. Of interest, in patients with PVT or underlying liver disease the diagnosis of certain thrombogenic factors may be impaired. Firstly, decreased hepatic synthetic function may result in lower plasma levels of protein C, protein S and antithrombin, thereby potentially masking a true deficiency or leading to an incorrect diagnosis of natural anticoagulant deficiency.³⁶ Secondly, characteristic features of an MPD (e.g. elevated platelets or haemoglobin) may be absent due to splenomegaly or haemodilution.³⁷ The latter diagnostic problem can be solved by performing a bone marrow biopsy or by assessing the presence of endogenous erythroid colony formation.³⁸ Furthermore, the diagnosis of MPD has recently been facilitated by the discovery of the V617F mutation of the Janus Kinase 2 (JAK2), a tyrosine kinase.³⁹ In patients with polycythaemia vera it has been shown that approximately 95% carry the JAK2 mutation; for essential thrombocythaemia and myelofibrosis this mutation is present in 50 to 60% of patients.⁴⁰ Because the JAK2 mutation is not found in healthy controls, it has been applied as a screening marker for MPD. In several studies of patients with noncirrhotic nonmalignant PVT, 20 to 35% of the cases were JAK2 positive, underlining that MPDs are a major risk factor for the development of PVT.⁴¹⁻⁴³

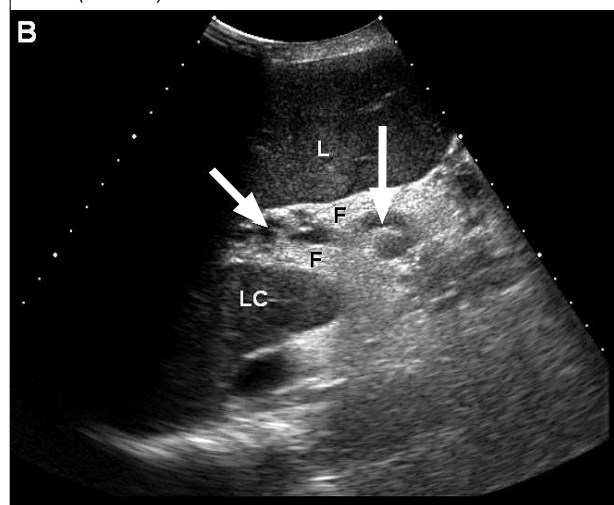
Chronic PVT

Whereas many patients will display some symptoms associated with PVT, a number of patients are completely asymptomatic.^{3,16} These patients are often only diagnosed by coincidence or later on when complications of chronic PVT occur. In response to thrombosis of the portal vein, portoportal and portosystemic collateral veins will develop to compensate for the decreased portal blood flow.^{44,45} These collaterals may be present within several days after the venous occlusion and are eventually found in nearly all patients with a complete obstruction of the portal vein.⁴⁶ However, the amount, size and localisation of collaterals differ strongly between patients. On imaging, the presence of a network of collateral vessels around the portal vein, a so-called portal cavernoma, is a typical feature of chronic PVT.⁴⁷ Moreover, in patients with long-standing thrombosis the portal vein itself often becomes a fibrotic cord and may be difficult to visualise (*figure 2*). Besides the development of collaterals, another compensatory mechanism that takes place is dilatation of the hepatic artery.⁴ Nevertheless, despite the fact that hepatic blood flow is only minimally decreased as a result of these haemodynamic changes, portal venous pressure is inevitably increased. Therefore, complications related to portal hypertension, such as splenomegaly and gastro-oesophageal varices, are the main features of patients with chronic PVT. At diagnosis of PVT, more than half of the patients will already have varices or signs of portal hypertensive gastropathy.^{10,48,49}

Figure 2A. Doppler ultrasound of a patient with chronic portal vein thrombosis depicting a network of collateral vessels (arrows) and some fibrosis (F) in the area of the portal vein



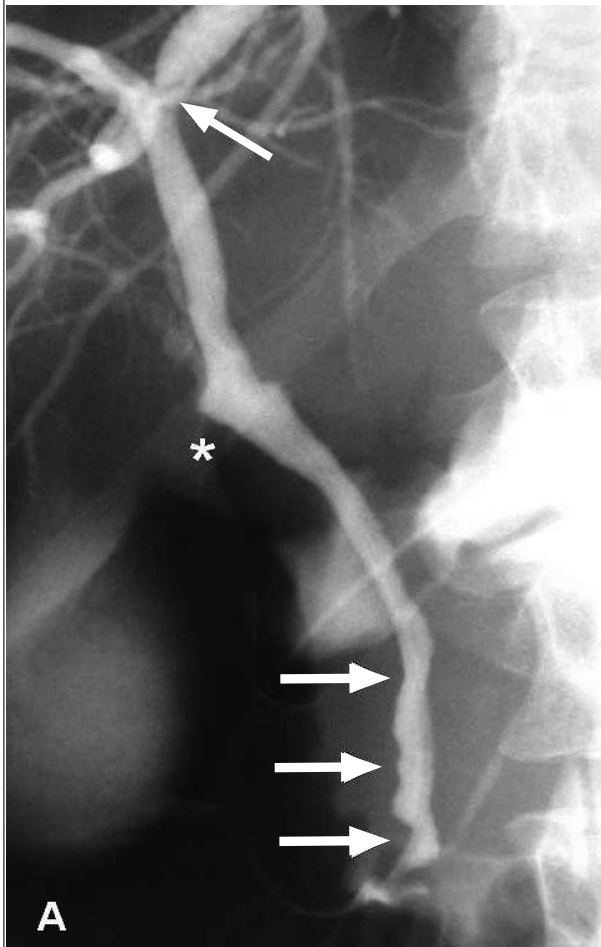
Figure 2B. Ultrasound image displaying the typical fibrotic transformation of the portal vein in chronic PVT; between the left lobe of the liver (L) and the lobus caudatus (LC), a marked fibrotic streak (F) can be visualised surrounding a meandering collateral vein (arrows)



Furthermore, in 20 to 40% of cases, an episode of gastrointestinal bleeding will be the presenting symptom of an underlying chronic PVT.^{3,16}

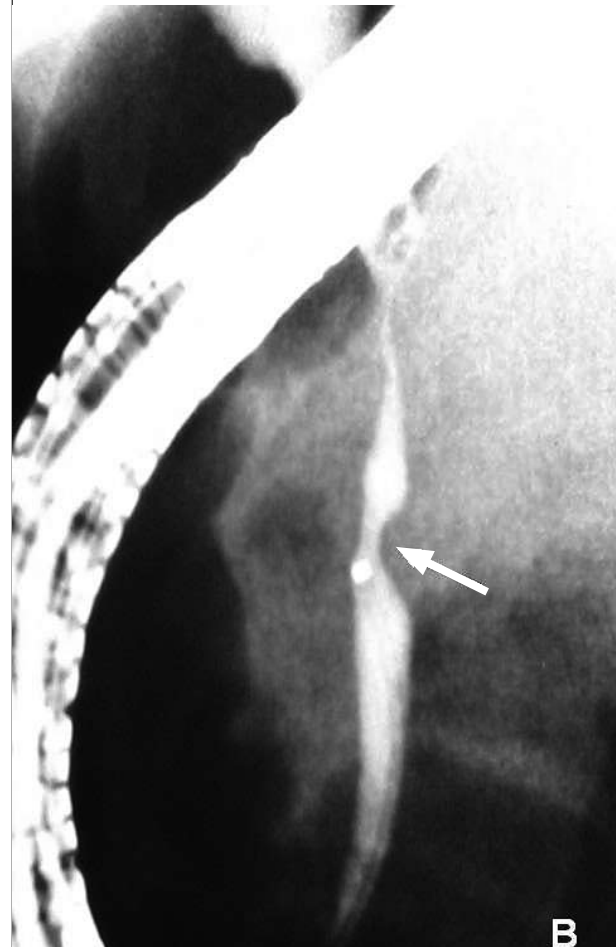
In addition to complications of portal hypertension, two other potential consequences of chronic PVT are intestinal ischaemia and portal biliopathy. As in patients with acute PVT, there is also a minor risk of intestinal ischaemia and bowel infarction in chronic PVT if there is secondary extension of thrombosis into the superior mesenteric vein. The other complication, portal biliopathy, denotes structural abnormalities of the intrahepatic or extrahepatic biliary

Figure 3A. Endoscopic retrograde cholangiography in a patient with symptomatic portal biliopathy



There is an undulating contour of the distal common bile duct (arrowheads) and more proximally marked angulation (*). Slight stenosis at the origin of the marginally dilated left hepatic duct (arrow).

Figure 3B. Smooth indentation of the common bile duct (arrow) in a patient with portal biliopathy



tree that are related to the presence of a portal cavernoma (figure 3).⁵⁰ These changes are most likely the result of either direct compression of bile ducts by the portal cavernoma or ischaemic structuring. In the majority of patients with chronic PVT a certain degree of biliary tree involvement can be demonstrated,^{51,52} but most remain asymptomatic. Clinical manifestations such as jaundice, cholangitis or cholecystitis are present in approximately 10 to 20% of cases, especially in patients of older age and with longer disease duration.^{53,54}

TREATMENT

Acute PVT

The management of patients with acute PVT is based on: (1) prevention of further thrombosis and therapy aimed at recanalisation, (2) treatment of complications (e.g. bowel infarction) and concurrent disease and (3) identification and, if possible, treatment of underlying (thrombophilic)

risk factors. Although no controlled studies have been performed, there is convincing evidence that rapid initiation of anticoagulation therapy results in either complete or partial recanalisation in a significant number of patients. Several retrospective series and a recent prospective study have all shown a beneficial effect of anticoagulation in patients with noncirrhotic nonmalignant PVT, with recanalisation rates of approximately 45%.^{30,35,48} Spontaneous improvement of portal vein patency was rarely seen in these studies. Therefore, the current consensus indicates that all patients with acute PVT should be treated with anticoagulation when there are no contraindications.⁵⁵ A minimal treatment duration of three months is advised but, as with venous thrombosis at other sites, this could be extended to six months. Moreover, in patients with proven systemic thrombophilia life-long anticoagulation therapy may be warranted due to the increased risk of new thrombotic events.^{28,48,55}

Apart from anticoagulation, several other treatment modalities have also been employed to achieve

recanalisation of the obstructed portal vein. A number of case reports have successfully demonstrated the use of local thrombolysis in the early phase of PVT.^{56,57} Recanalisation has also been described after surgical thrombectomy or with percutaneous transhepatic angioplasty (PTA).^{58,59} Nevertheless, experience with these techniques is limited and the risk of procedure-related complications and mortality is high.^{60,61} Consequently, their role in the treatment of acute PVT is still highly controversial.

In addition to its effect on recanalisation, anticoagulation should also be initiated in the acute phase of PVT to prevent extension of the thrombosis. Extensive thrombosis of the mesenteric veins is mostly symptomatic and carries a high risk of intestinal ischaemia.¹⁶ Symptoms that may be present are severe abdominal pain and bloody diarrhoea. When intestinal infarction is suspected, immediate surgical intervention is required to resect necrotic parts of the bowel. If left untreated, bowel ischaemia can lead to major complications such as intestinal perforation, shock, multi-organ failure and even death.³⁴

Chronic PVT

Treatment and prevention of variceal bleeding

For patients with chronic PVT, therapy is mainly aimed at the treatment and prevention of complications of portal hypertension. Bleeding from gastro-oesophageal or ectopic (e.g. duodenal or rectal) varices is the most important complication of PVT-induced portal hypertension. Around 50% of patients will already have signs of varices at diagnosis and for that reason endoscopic screening for the presence of varices should be part of the diagnostic work-up in all patients with (chronic) PVT. In the case of noncirrhotic nonmalignant PVT, approximately 30% of patients will experience one or more episodes of gastrointestinal bleeding during follow-up.^{3,49} When an underlying cirrhosis is present the incidence of variceal bleeding is even higher.³ The risk of bleeding is also increased in patients with large varices at diagnosis, especially for those who do not receive adequate prophylactic treatment.^{48,49} Despite the serious nature of complications, no controlled studies have been performed addressing the optimal management of variceal bleeding in patients with PVT. Therefore, current guidelines are mainly based on data from studies in patients with portal hypertension caused by liver cirrhosis, in the absence of PVT.⁵⁵ As has become clear from these studies, primary prevention of bleeding is recommended in patients with large (>5 mm) varices.⁶² Treatment with nonselective β -blockers and endoscopic band ligation are equally effective and both significantly reduce the risk of a first bleeding episode.⁶³ It has not been established which therapy should be preferred in patients with PVT, but pharmacological treatment with β -blockers is probably more cost-effective. Endoscopic treatment as primary prevention could then be reserved for those patients with intolerance or contraindications to β -blockers.

When prevention fails or when a patient presents with variceal haemorrhage, endoscopic therapy is the mainstay of treatment. Variceal band ligation is the preferred treatment modality for acute bleeding episodes but endoscopic sclerotherapy may also be applied.⁵⁵ For acute bleeding from gastric fundal varices, endoscopic variceal obturation with tissue adhesives seems to be most effective to control bleeding.⁶⁴ Other, more general, measures in patients with gastrointestinal haemorrhage may include volume resuscitation, blood transfusions and admission to an intensive care unit. Furthermore, it has been shown that additional treatment with vasoconstrictors and antibiotics also has a beneficial effect on complications and survival.⁶⁵ After a first episode of variceal bleeding has been controlled, therapy is aimed at prevention of further events. In patients with cirrhosis and portal hypertension, treatment with β -blockers and endoscopic band ligation can both reduce the rate of rebleeding.⁶⁶ Combined therapy of pharmacological treatment and endoscopy is even more effective in the secondary prevention of variceal bleeding.⁶⁷ In patients with PVT there have been a few studies addressing the prevention of rebleeding, specifically with endoscopic therapy. It was shown that endoscopic eradication of varices in patients with noncirrhotic nonmalignant PVT significantly reduced the risk of rebleeding.^{68,70} The rate of rebleeding was reported to be 23% in the first year,⁷⁰ which compares favourably with a rebleeding rate of approximately 31% in cirrhotic patients treated with endoscopic band ligation.⁷¹ Studies investigating the effect of β -blockers on the prevention of rebleeding in patients with PVT have not been performed and their role in the secondary prophylaxis of variceal bleeding in these patients is therefore still unclear.⁵⁵ Many patients with PVT-induced portal hypertension can be adequately managed with pharmacological or endoscopic treatment. However, when these therapeutic options fail and in patients with recurrent variceal bleeding, a shunting procedure could be considered. Surgical shunts, preferably a distal splenorenal shunt, have proven to give durable decompression of the portal venous system.⁷² Disadvantages that hamper the widespread application of these procedures are the considerable rates of morbidity and mortality and the high risk of shunt thrombosis.^{13,73} As a less invasive option, recent interest has gone out to the use of a transjugular intrahepatic portosystemic shunt (TIPS). Several studies have reported the successful use of TIPS in the management of patients with PVT.⁷⁴⁻⁷⁶ Nevertheless, a TIPS can only be performed in selected patients, as in many cases the procedure is technically not feasible due to extensive thrombosis (e.g. involving the splenic and mesenteric veins) or an inability to catheterise either the portal vein itself or collaterals forming the portal cavernoma. Future studies will have to determine the exact role of TIPS in the treatment of portal hypertension associated with PVT.

Other therapeutic measures

Treatment of portal biliopathy is only indicated in symptomatic patients. Endoscopic therapy with or without stent placement is effective in most cases of biliary obstruction or biliary stone formation.⁷⁷ When symptoms persist, a surgical intervention may be needed, aimed at the management of portal hypertension. A few studies performed in patients with portal biliopathy as a result of PVT have illustrated that symptoms can be relieved with a portosystemic shunting procedure.^{78,79} This diminishes the need for a secondary surgical bilioenteric anastomosis, which is associated with a high morbidity and mortality in these patients due to the extensive network of collaterals frequently surrounding the biliary structures.⁸⁰

Whereas the role of anticoagulation has been quite well established in the treatment of patients with acute PVT, there is still much debate concerning its place, if any, in the management of chronic PVT. The significant risk of bleeding complications from gastro-oesophageal varices is often seen as a contraindication. Nevertheless, the high prevalence of systemic thrombophilia would support treatment with anticoagulation, as it has been reported that patients with PVT and an underlying thrombogenic risk factor have an increased risk of developing further thrombotic events.^{29,48,49} Moreover, it was shown that anticoagulation therapy decreased the incidence of new thrombotic episodes in these patients whilst the risk and severity of variceal bleeding was not altered.⁴⁹ This would support the use of anticoagulation in patients with chronic PVT and proven thrombophilia. Whether anticoagulation should be considered in patients with PVT and underlying liver cirrhosis is even less clear. One study has suggested that anticoagulation therapy may prove useful in a subgroup of patients with cirrhosis and PVT that are candidates for liver transplantation.⁸¹ The presence of PVT in patients undergoing liver transplantation is associated with more complex surgical procedures and an increased rate of complications.^{82,83} Treatment with anticoagulation in cirrhotic patients with PVT awaiting transplantation resulted in recanalisation in 42% of cases and successfully prevented extension of thrombosis.⁸¹ Still, despite these favourable results of anticoagulation, evidence is minimal and more studies are needed to define whether treatment with anticoagulation truly has a beneficial effect in patients with chronic PVT. Current consensus, solely based on expert opinion, indicates that life-long anticoagulation therapy should be considered in patients with PVT in whom an underlying thrombophilic risk factor has been identified.⁵⁵

PROGNOSIS

The prognosis of patients with PVT is mainly determined by the underlying cause of thrombosis and not by the

complications of portal hypertension.^{3,10} Whereas in earlier studies many patients died as a result of variceal bleeding,⁸⁴ recent data suggest that mortality related to gastrointestinal haemorrhage is uncommon.⁴⁸ In a large cohort of 172 patients with PVT, death due to variceal bleeding occurred in 2% of the patients.¹⁰ Furthermore, in a recent short-term prospective study in patients with noncirrhotic nonmalignant PVT, no deaths due to variceal bleeding were reported.³⁵ The prognosis of PVT patients without underlying cirrhosis or malignancy can therefore be considered as good, with five- and ten-year survival rates of 90 and 80%, respectively.¹⁰ Outcome is worse in patients with liver cirrhosis because in this group liver function is already impaired and there is a higher risk of (liver-associated) complications and liver decompensation. Survival after liver transplantation was shown to be significantly lower in cirrhotic patients with concomitant PVT as compared with cirrhotic patients without PVT.⁸¹ Clearly, the presence of an underlying malignancy also substantially affects survival. It has been reported that patients with HCC who develop PVT during the course of the disease have a very poor prognosis.²⁸ In one study, five-year survival of PVT patients with malignancy was only 8%.¹⁰ Another factor that has a negative impact on survival is intestinal ischaemia complicated by bowel infarction. In patients with mesenteric vein thrombosis mortality rates may vary between 20 and 50%.³⁴ Conversely, underlying systemic risk factors do not seem to influence prognosis, although long-term follow-up data of patients with PVT and known thrombophilia are lacking. A recent study demonstrated that the presence of an MPD does not affect five-year survival rates.²³

CONCLUSION

Thrombosis of the portal vein often has a multifactorial aetiology. Presentation is highly variable and the clinical course is relatively benign, but dependent on the underlying cause. Acute and chronic PVT are two distinct disease entities that require a somewhat different treatment approach. Anticoagulation is the mainstay of treatment in acute PVT whereas therapy for chronic PVT is guided by the presence and severity of complications related to portal hypertension. Because controlled studies in patients with PVT are not available, gastro-oesophageal varices should be treated as in patients with liver cirrhosis-induced portal hypertension. Despite recent advances, many aspects of the (multifactorial) aetiology and management of PVT are still unclear. More studies are needed to further elucidate the role of anticoagulation in patients with chronic PVT and the role of different therapeutic options in the treatment and prevention of variceal bleeding.

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