

Management of patients with (non tumoural) porto-mesenteric vein thrombosis

1 Scope

- For patients being managed by the Hepatology/Liver Transplant teams in Addenbrooke's Hospital

2 Purpose

- To provide an evidence base/rationale for the clinical management of patients with porto-mesenteric vein thrombosis.

3 General recommendations

- This is a heterogeneous cohort and many patients will benefit from a multi-disciplinary approach including the Hepatology/Surgical/Radiology/Haematology teams.
- The aim of treatment is recanalisation - to reduce the likelihood of short term complication (i.e. bowel infarction) and long term complication (i.e. complications of portal hypertension).
- Factors that will influence treatment include: acute vs chronic; vessel involvement; presence or absence of cirrhosis; underlying precipitant; clinical picture.
- All patients with an "unprovoked" porto-mesenteric vein thrombosis (PMVT) should have a procoagulant screen including the following: protein C/S; lupus anticoagulant, anti-cardiolipin and anti-beta2 glycoprotein antibodies; JAK2-mutation (if negative CALR exon 9 mutation); Factor V Leiden and Prothrombin genotype; PNH screen; blood film (+/- total homocysteine level). In provoked PMVT, the thrombophilia screen should be left to the discretion of the portal hypertension clinic or haematology.
- The evidence base is suboptimal with few RCTs and studies mixing acute and chronic PMVT, partial vs complete thrombosis, and thrombus burden.

4 Factors that influence the recanalisation rate

4.1 Precipitant

Reduced flow velocity and bacterial translocation probably play a key role in the development of PMVT complicating cirrhosis (14). The 1, 5 and 10 year cumulative incidence of portal vein thrombosis (PVT) in these patients has been reported to be 13%, 20% and 39% respectively (3). Incidence of PMVT correlates with the severity of liver disease.

In the absence of cirrhosis, the most common precipitant is usually temporary i.e. intra-abdominal inflammation/infection/surgery, the oral combined contraceptive pill. A procoagulant disorder is identified in ~50%. In 25% there is no clear causal factor (4).

4.2 Natural history

In untreated cirrhotic patients (i.e. absence of anticoagulation), 42% will demonstrate some degree of PVT recanalisation, and 33% will have complete recanalisation, whilst PVT progresses in 33% (5). In symptomatic non cirrhotics not receiving anticoagulation, spontaneous recanalisation is the exception (6).

4.3 Duration

Maximal recanalisation with anticoagulation probably occurs by 6 months after onset based on a prospective study in non cirrhotics (4). Anticoagulation beyond 6 months is therefore only given to prevent thrombosis extension or extra-splanchnic thrombosis where there are persistent risk factors (e.g. cirrhosis, procoagulant disorder) (2).

4.4 Vessel involvement/severity

In non cirrhotics treated with anticoagulation, the rate of recanalisation of the portal vein or its two main branches, splenic vein and superior mesenteric vein is 38%, 54% and 61%, respectively – the portal venous system becomes completely patent in 20%. Factors that have been found to be associated with failure to recanalise are splenic vein obstruction, superior mesenteric vein obstruction, ascites (including small volume on imaging) and JAK2 mutation positive (4). In another study, an ALT >30 u/L, hypoalbuminaemia, mesenteric vein thrombosis and the absence of abdominal inflammation were linked with an increased risk of death (7). Logically, the more extensive the clot burden and the greater the clinical impact (i.e. abdominal pain, free fluid), the lower the likelihood of recanalisation.

4.5 Anticoagulation

Loffredo's recent problematic meta-analysis of predominantly non RCT data in cirrhotics found that patients who received anticoagulation had a 71% at least partial recanalisation rate (vs 42% in patients not receiving anticoagulation), a

53% total recanalisation rate (vs 33%), and a 9% clot extension rate (vs 33%). There was no difference in the overall bleeding complication rate between the two groups, and spontaneous variceal bleeding was less likely to occur in those receiving anticoagulation (5). In this paper, low molecular weight heparin but not warfarin was associated with total recanalisation.

In non cirrhotics, anticoagulation (heparin followed by warfarin) was associated with a partial and total recanalisation rate of 38-61% and 20%, respectively (4) (see section 4.4).

4.6 TIPSS

TIPSS alone (i.e. in the absence of anticoagulation) (80% covered stent) for variceal haemorrhage/ascites in patients with portal venous system thrombosis (56% of patients had >50% luminal occlusion) is accompanied by a total recanalisation rate of 57%, and a "marked decrease" in thrombus burden in 30%. In this study, of the 40 patients who demonstrated complete recanalisation, the recanalisation rate was 53%, 70% and 99% at 6, 12 and 24 months after TIPSS, respectively. Only 5% patients experienced recurrence of thrombosis during long term follow-up thereafter. Factors associated with recanalisation after TIPSS placement were single vessel involvement, <25% luminal occlusion, de novo diagnosis and absence of varices (8).

A single suboptimal RCT of TIPSS vs band ligation/non-selective beta-blocker (NSBB) for prevention of variceal bleeding in patients with cirrhosis and PVT observed a 65% recanalisation rate in the TIPSS arm and 20% in the non TIPSS arm. In this study anticoagulation was started immediately after the TIPSS/variceal eradication (9).

Local data suggests that in select patients with non-cirrhotic acute symptomatic PMVT, 50% treated with systemic recombinant tissue plasminogen activator (r-tPA) alone recanalise, compared to 100% of those treated with systemic r-tPA followed by TIPSS/thromboaspiration (abstract). Successful intervention in chronic PMVT has also been reported (10).

5 Risk benefit ratio

Management recommendations to aid recanalisation must take into account the risk benefit ratio in the individual. Portal venous system thrombosis in acute pancreatitis and cirrhosis requires special mention.

5.1 Acute pancreatitis

Portal venous system thrombosis complicates up to 15-20% of severe acute pancreatitis affecting most commonly the splenic vein, followed by portal vein and then superior mesenteric veins; and is associated with the presence, location and extent of pancreatic necrosis. Spontaneous recanalisation is rare (11). Full anticoagulation however remains controversial because of the risk of bleeding. A total of 25 patients have been reported who have been anticoagulated in the context of acute pancreatitis: in one study 3 of 7

anticoagulated patients had a haemorrhagic complication; in another 0 of 15 patients demonstrated bleeding (11,12,13).

5.2 Cirrhosis

PMVT recanalisation will aid technical feasibility of liver transplantation; however it remains unclear whether recanalisation impacts on prognosis in non transplant candidates. On the other hand, there does not appear to be an increased bleeding risk with anticoagulation in this patient group. Baveno VI recommend anticoagulation in liver transplant candidates only – in non-transplant candidates no recommendation has been made because of insufficient evidence (2). All patients should receive appropriate prophylaxis of variceal haemorrhage (band ligation or non-selective beta blocker) prior to initiation of anticoagulation (1).

6 Recommended management to aid recanalisation

6.1 Non cirrhotic acute PMVT

Patients will present with abdominal pain. Clinical findings may include pyrexia, elevated inflammatory markers and a low grade transaminitis. Blood lactate is usually normal unless there is bowel ischaemia.

All patients should have a triple phase CT and procoagulant screen (Section 3).

6.1.1 Anticoagulation alone

Most patients will be treated with anticoagulation alone. The usual approach is low molecular weight heparin for 2 weeks followed by warfarin with a target INR 2-3.

Drug absorption may feasibly be impaired in extensive acute portal venous system thrombosis and as such a longer duration of low molecular weight heparin, potentially up to 3-4 months, may be sensible in some patients (no evidence base).

High risk of clot extension patients may benefit from the addition of aspirin 75mg/day (no evidence base) e.g. JAK2 positive, patients undergoing aggressive intervention (Section 6.1.2).

Any underlying prothrombotic condition should be treated.

Data is lacking regarding the use of the Direct Oral Anticoagulants (DOACs) in this setting; however 3 non cirrhotic patients have been through the unit in recent past having developed de novo acute PMVT whilst on Rivaroxaban/Dabigatran. The recommendation therefore is that the DOACs should not be used for the treatment of non-cirrhotic acute PMVT until further information is available.

Duration of treatment:

- Temporary precipitant (e.g. intra-abdominal infection/inflammation) – 6 months of anticoagulation.
- Persistent procoagulant condition – long term anticoagulation unless bleeding risk precludes treatment.

A repeat CT 6 months after PMVT onset is recommended to determine the maximal extent of recanalisation, and the new baseline.

For patients who do not recanalise see Section 6.2 for the management of chronic PMVT.

6.1.2 r-tPA and TIPSS/thromboaspiration/catheter directed thrombolysis

A subgroup of patients will be selected by the Consultant Hepatologist for more aggressive intervention taking into account the factors detailed in Section 4. Generally speaking, this treatment option should be considered in patients with recent onset thrombosis (<4 weeks), abdominal pain and an extensive clot burden in the absence of contraindication – when the aim is to prevent bowel infarction or to reduce the likelihood of portal hypertension related complications. A transaminitis and/or free fluid on imaging may also point towards a worse prognosis.

The treatment protocol is as follows and summarised in Appendix 1. It should be led by the Consultant Hepatologist in collaboration with the Transplant Surgeons/Radiologists/Haematologists:

- All patients require an HDU level bed (F5/IDA, or RRT depending on severity of illness) and central intravenous access.
- Give broad spectrum antibiotic cover for the duration of treatment.
- Ideally, recanalisation should be attempted with systemic intravenous Alteplase (r-tPA) for 72 hours as per protocol, unless contraindication (Appendix 1), before progressing to TIPSS/thromboaspiration if significant persistent thrombosis. During this phase a standard systemic unfractionated heparin intravenous infusion is usually continued alongside the Alteplase.
- Repeat triple phase liver CT at the end of 72 hours of Alteplase.
- If persistent portal venous system thrombosis, depending on clot burden, consider TIPSS/thromboaspiration/catheter directed thrombolysis.
- In most cases, TIPSS/thromboaspiration will be followed by 24-72 hours of local catheter directed r-tPA/unfractionated heparin administration led by the Interventional Radiologist. There may be check venograms/further intervention led by the Interventional Radiologist. A standard systemic unfractionated heparin intravenous infusion should be continued during this phase alongside any local catheter directed r-tPA/heparin, except for 4 hours prior to and during TIPSS insertion or further intervention.
 - Note catheter directed thrombolysis is beyond the scope of this guideline.
- Following removal of the portal vein catheter, in the absence of bleeding complication:
 - Start therapeutic low molecular weight heparin
 - Add aspirin 75mg/day 24 hours later

- Repeat triple phase liver CT prior to hospital discharge to determine new baseline
- Following hospital discharge
 - Therapeutic low molecular weight heparin and aspirin 75mg/day should be continued for 3-4 months unless contraindicated - high risk phase for clot extension and potential impaired bowel absorption.
 - Thereafter, long term warfarin +/- aspirin. DOACs are not currently recommended (see Section 6.1.1 and 6.3.1).
 - Outpatient monitoring via CONREV3 if possible.
 - Repeat triple phase liver CT at 3 months (when there remains the risk of clot extension) and then 6 months (to determine long term baseline).
 - Variceal screening in patients with persistent portal venous system thrombosis.
 - Haematology opinion and optimisation of underlying procoagulant disorder.

6.2 Non cirrhotic chronic PMVT

Many patients will be diagnosed with non cirrhotic chronic PMVT incidentally on cross sectional imaging. Others may present with complications of portal hypertension.

Newly diagnosed patients can be referred to the portal hypertension clinic (CONREV3).

A full procoagulant screen should be performed (Section 3).

In the absence of a procoagulant condition, anticoagulation is not recommended in established non cirrhotic chronic PMVT. The risk benefit ratio of anticoagulation should be reconsidered however if a procoagulant condition develops e.g. portal biliopathy with recurrent cholangitis.

All patients should be screened for varices (Section 7).

6.3 Cirrhotic PMVT

Many patients will be diagnosed with cirrhotic chronic PMVT incidentally on cross sectional imaging. Others may present with complications of portal hypertension.

A full procoagulant screen should be performed (Section 3).

All patients should be screened for gastro-oesophageal varices (Section 7).

6.3.1 Anticoagulation

Consider long term anticoagulation in liver transplant candidates depending on the risk benefit ratio (Section 5.2).

Low molecular weight heparin may be superior to warfarin (5), and is preferred in patients on the liver transplant waiting list (split dose as per the "Management of patients undergoing liver transplantation" handbook on Merlin). Warfarin is an appropriate alternative.

There is limited data regarding the use of the DOACs in patients with cirrhosis and as such are not recommended in routine practice (15,16). The following should be borne in mind when considering these agents:

- There are safety concerns regarding rivaroxaban and apixaban in Child's B/C cirrhosis – partly liver cleared.
- Rivaroxaban and Apixaban have decreased *in vitro* anticoagulant potency in patients with cirrhosis compared to healthy controls (17).
- For dabigatran, the pharmacokinetics in Child's B cirrhosis are the same as in healthy controls and mainly cleared by the kidneys; however *in vitro* data suggests that cirrhotics may have increased sensitivity to the effects (17).
- Gastrointestinal bleeding concerns have been raised for all agents potentially relating to poor bioavailability and increased concentrations within the bowel lumen.
- Two patients with cirrhosis have been through the unit in recent past having developed de novo acute PMVT or clot extension whilst on rivaroxaban.

In short, anticoagulation should be considered on a case by case basis. Outwith PMVT, the DOACs may be appropriate in patients with Child's A cirrhosis for the management of atrial fibrillation and pulmonary emboli where there is a good evidence base and the patient is intolerant of warfarin. The DOACs are not recommended in patients with Child's B/C cirrhosis and in peri-hepatic thrombosis (PMVT or Budd Chiari syndrome).

6.3.2 TIPSS

Some cirrhotic patients with complicated acute PMVT may benefit from TIPSS, particularly future liver transplant candidates. Thromboaspiration should be considered perhaps more carefully in this cohort – the resultant increased flow velocity may be enough to clear the clot without further intervention, and there is a theoretical risk of precipitating thrombosis via endothelial activation. Anticoagulation should still be given if there is not an active bleeding risk (may increase the likelihood of recanalisation; risk of pulmonary emboli). Patients should be counselled preTIPSS on the risk of pulmonary emboli as well as encephalopathy.

7 Management of varices in PMVT

7.1 Surveillance

All patients with established occlusive thrombosis should undergo gastro-oesophageal variceal surveillance.

Non cirrhotic patients who do not demonstrate recanalisation should be screened for varices within 6 months of the acute episode. In the absence of varices, a repeat gastroscopy at 12 months and then 2 years thereafter is recommended (2). Long term variceal surveillance may be tailored to the individual and may not need to be as rigid as in cirrhosis.

All cirrhotic patients should undergo standard variceal surveillance. The screening gastroscopy should be repeated in the face of a newly diagnosed PMVT.

7.2 Management

There is insufficient data to make specific recommendations for the management of varices in portal venous system thrombosis.

PMVT

- Baveno VI advise following the guidelines for cirrhosis (2).
- In the primary prophylaxis of oesophageal varices a non selective beta-blocker (NSBB) may be adequate even if being anticoagulated (given that in cirrhotic patients NSBB is equivalent to band ligation in the prevention of first oesophageal variceal haemorrhage); although in patients receiving anticoagulation with higher risk varices band ligation may be sensible.
- Carvedilol may be superior to propranolol – owing to reduced portocolateral resistance secondary to additional alpha1 blockade.
- In the primary prophylaxis of gastric/ectopic varices, usually no treatment is recommended although NSBBs/endoscopic therapy may be considered in high risk cases.
- Varices that have bled should be managed as for cirrhotic patients.
- In refractory variceal bleeding there may be an option for radiological intervention, surgical shunt or liver alone/multivisceral transplantation.
- Anecdotally NSBBs may also be helpful in patients with low volume ectopic variceal bleeding or recurrent iron deficiency anaemia secondary to portal hypertensive gastropathy/enteropathy ooze.

Splenic vein thrombosis

- There is no role for NSBBs in segmental portal hypertension secondary to splenic vein thrombosis.
- Endoscopic therapy is 1st line treatment for varices that have bled.
- Splenectomy should be considered in complicated splenic vein thrombosis.

Varices are not a contra-indication to anticoagulation, but patients with varices should receive appropriate variceal bleeding prophylaxis. If a variceal band ligation programme is initiated, the risk benefit ratio will often favour continuing anticoagulation before variceal eradication (low molecular weight heparin is the preferred option logistically during this phase).

8 Associated documents

Anticoagulation: adult inpatient initiation guideline (November 2018)
Unfractionated heparin intravenous infusion protocol
Management of patients undergoing liver transplantation Handbook
(January 2017)

9 References

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10 Document Management

Is the document COVID-19 related	No
Name of Document	Management of patients with (non tumoural) porto-mesenteric vein thrombosis
What document or version number does this document replace (if existing published document)	Version 1
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Does it need to be displayed on the Addenbrooke's public website (patient information leaflets only)	NA

Appendix 1 – Systemic Alteplase protocol for patients with acute porto-mesenteric vein thrombosis

(adapted from Royal Free Hospital protocol)

1.1 Indication

- A subgroup of patients with complicated acute porto-mesenteric vein thrombosis where standard anticoagulation has not been effective or clot resolution is not amenable to surgical intervention.
- Restricted to patients selected by the Consultant Hepatologist and managed in conjunction with the Surgeons, Radiologists, Haematologists.

1.2 Method of action

- Alteplase is a thrombolytic agent that induces the conversion of plasminogen to plasmin leading to the dissolution of the fibrin clot.

Contra-indications

- Known bleeding disorder
- Fibrinogen of less than 1.5 g/L or platelet count of $< 50 \times 10^9/L$
- Current active bleeding
- Recent major trauma/surgery/head injury (preceding 3 weeks)
- Ischaemic stroke or TIA in preceding 6 months
- Previous cerebral haemorrhage at any time
- CNS trauma/neoplasm
- Acute pancreatitis
- GI bleeding within last 3 months
- Aortic dissection
- Non compressible puncture (e.g. liver biopsy, lumbar puncture)
- Bacterial endocarditis or pericarditis
- Pregnancy or within 1 week post partum
- Refractory hypertension (Sys>180 mmHg or Dias>110 mmHg)
- Refractory resuscitation
- Allergic reaction to alteplase or excipients (arginine, dilute phosphoric acid or polysorbate 80)

Cautions

- Abnormal baseline coagulation – please discuss with Haematology consultant on call
- Liver disease (at the discretion of the Consultant Hepatologist)

1.3 Practicalities

- HDU level bed for monitoring of bleeding complications – F5/IDA or RRT.
- Central intravenous access.
- Broad spectrum antibiotic cover.
- +/- Systemic iv heparin - see unfractionated heparin IV infusion protocol
- Written patient consent.

1.4 Dose

- 0.05mg/kg/hour (max 4mg / hour) as an IV infusion over 72 hours
- Reconstitute the dose (made up of 20mg and 50mg vials) of alteplase with equal volume of WFI to give a concentration of 1mg/ml – this preparation is stable at room temperature for 8 hours and needs to be changed at this interval. Reconstituted vials can be kept in the fridge for 24 hours and used to prepare the next dose.
- e.g. if the patient is 70kg , the dose over 8 hours would be $0.05 \times 70\text{kg} \times 8 \text{ hrs} = 28\text{mg}$. This would require 28ml from a 50ml vial of Alteplase (reconstituted with 50ml WFI) to be given over 8 hours using a syringe driver.

1.5 Monitoring requirements and frequency		
	Routine monitoring	Increased monitoring where: <ul style="list-style-type: none"> • Signs of continuous ooze • Fibrinogen is < 2.5 g/L • Platelet count < 100 x 10⁹/L
Full Blood Count, Prothrombin Time, and fibrinogen	12 hourly	6 hourly
D-dimer Plasminogen	Daily*	Daily*
Signs of bleeding from venepuncture sites	4 hourly	4 hourly
ROTEM / TEG - liaise with haemophilia consultant regarding availability	Daily	Daily

*Within working hours 9-5pm

1.6 Stopping criteria

- Fibrinogen decreases to < 2 g/L
- Platelet count < 50 x 10⁹/L
- Continuous bleeding from venepuncture sites
- Massive haemorrhage

1.7 Efficacy monitoring

- Arrange for Doppler studies for recanalization and abdominal contrast enhanced CT at completion of 48 hours of alteplase or earlier if condition changes.
- At review, options include:
 - Catheter directed thrombolysis
 - Continue infusion
 - Start therapeutic LMWH - liaise with haemophilia consultant for appropriate dosing regimen.

1.8 Management of haemorrhage

- Fresh frozen plasma x 3 units for neutralising any plasmin
- Fibrinogen concentrate to keep fibrinogen above 2 g/L
- Red cells and platelets as needed
- Tranexamic acid 1 g IV
- Management of the bleeding point