Venous Thrombosis in Unusual Sites: A practical review for the Hematologist.


1. Division of Hematology-Oncology, Oregon Health & Science University, Portland OR
2. Department of Internal Medicine, Oregon Health & Science University, Portland OR
3. Division of Gastroenterology, Oregon Health & Science University, Portland OR
4. Division of Vascular Surgery, Oregon Health & Science University, Portland OR

Running Title: Venous Thrombosis in Unusual Sites

Abstract

Corresponding Author:

Joseph J. Shatzel MD

Department of Hematology & Oncology

Oregon Health & Science University

3181 SW Sam Jackson Park Rd, Portland OR 97239

(503) 494-8311

shatzel@ohsu.edu

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ehj.13177

This article is protected by copyright. All rights reserved.
ABSTRACT

Thrombosis of unusual venous sites encompasses a large part of consultative hematology, and is encountered routinely by practicing hematologists. Contrary to the more commonly encountered lower extremity venous thrombosis and common cardiovascular disorders, the various thromboses outlined in this review have unique presentations, pathophysiology, workup and treatments that all hematologists should be aware of. This review attempts to outline the most up to date literature on cerebral, retinal, upper extremity, hepatic, portal, splenic, mesenteric and renal vein thrombosis, focusing on the incidence, pathophysiology, provoking factors and current recommended treatments for each type of unusual thrombosis to provide a useful and practical review for the hematologist.

KEYWORDS: Venous Thrombosis, Coagulation Disorder, Hypercoagulable, Anticoagulation

INTRODUCTION

Thrombosis of the deep veins of the lower extremities is a common, well studied illness, routinely encountered by many medical and surgical disciplines. Due to its high prevalence in multiple clinical settings, many physicians feel comfortable with the routine diagnosis and management of straightforward venous thromboembolism (VTE). Less commonly, thrombosis can occur at unusual venous sites including the veins within the central nervous system, abdomen, or within intra-abdominal organs. Thrombosis in these more unusual sites has significantly different and more obscure provoking factors, and in some instances heralds the onset of other occult illnesses, often compelling the physician to consider a unique workup and treatment plan.

While understudied, the current body of knowledge on these rare thromboses suggests that unique local and systemic factors are often at play, specific to each site of thrombosis. In this review, we have outlined the epidemiology, common provoking entities, pathophysiology, and treatment (Table
1) in these admittedly understudied illnesses in an attempt to make a practical review for the hematologist.

CEREBRAL VEIN THROMBOSIS

Cerebral venous thrombosis (CVT), including thrombosis of cerebral veins and major dural sinuses, can present with a variety of symptoms including headache, focal neurologic deficits, seizures, and progression to infarction or hemorrhage. \(^1,2\)

CVT is a rare entity accounting for less than 1% of all strokes. \(^3\) It is three times more common in women as compared to men, occurring at a much younger age on average in women (34 years vs 42 years). \(^4\)

In CVT, 85% of patients will have an identifiable risk factor, the most common of which are estrogen containing oral contraceptive use or pregnancy. \(^2\) Other rare causes include acquired thrombophilia, vasculitis, myeloproliferative neoplasms (MPNs), chronic inflammatory disorders, or local factors such as infection, malignancy, trauma or surgery. \(^2\)

Both cerebral vein and cerebral sinus thrombosis lead to increased venous pressure causing disruption of the blood brain barrier and subsequent vasogenic and cytotoxic edema. Obstruction of cerebral sinuses may also result in decreased cerebrospinal fluid absorption leading to increased intracranial pressure—worsening venular hypertension and contributing to parenchymal hemorrhage. \(^1\) Anticoagulation should be started immediately in patients with CVT, even in patients with CVT that has progressed to hemorrhage. Two studies compared outcomes in patients treated with anticoagulation vs placebo, one of which was halted early due to benefit in the anticoagulation arm. \(^5,6\) Meta-analysis of the two trials found a trend towards decreased mortality in the
anticoagulation arms which did not reach significance, likely due to the small size of the studies, and noted that no new intracranial hemorrhages occurred in any patient.\textsuperscript{7} In patients who present with CVT with secondary intracranial hemorrhage evidence still suggests a benefit to anticoagulation.\textsuperscript{8} Systematic review of multiple studies found that early partial or complete recanalization occurs in two-thirds of patients treated with anticoagulation and approximately 90\% of surviving patients recover fully or with only minor deficits.\textsuperscript{9} Alternative interventions exist including catheter directed thrombolysis, mechanical thrombectomy, or surgery, however data is limited on their use, and these measures are usually reserved for patients who deteriorate despite systemic anticoagulation.\textsuperscript{8}

The recurrence rate for patients with cerebral vein thrombosis is low, especially if there was a provoking factor in the initial thrombosis.\textsuperscript{10} For thrombosis related to estrogen or other provoking etiologies three months may suffice while for idiopathic thrombosis expert recommendations vary from six months to a year.\textsuperscript{11}

RETINAL VEIN THROMBOSIS

Retinal vein occlusion (RVO) is a sight threatening malady often presenting with acute painless unilateral vision loss, although occlusion of a branch retinal vein may be asymptomatic, or present with double vision, or hemianopsia.\textsuperscript{12} Large epidemiologic studies have noted a prevalence of retinal vein occlusion between 0.5\% in middle aged adults to as high as 4.6\% in patients over 80 years old, suggesting that in any given year several million adults are affected by this disease.\textsuperscript{13}

Unlike traditional venous thrombosis, the risk factors for RVO mimic those of small vessel arterial disease. Hypertension, diabetes mellitus, smoking and obesity have all been shown to increase the risk of RVO while increased physical activity, alcohol use and increase HDL have been suggested to
be protective.\textsuperscript{14,15} Open angle glaucoma and increased blood viscosity also appear to be risk factors.\textsuperscript{16,17}

The pathogenesis of RVO is not well understood. Branch retinal veins may get occluded as crossing arterioles become increasingly sclerotic and inflexible, compressing the relatively pliant vein.\textsuperscript{18} Furthermore, the central retinal vein and retinal artery share a common adventitial sheath leading some to suggest that arterial compression brought about by atherosclerotic disease may precipitate central RVO.\textsuperscript{19} This effect may be compounded by unique properties of the retinal veins which predispose them to arterial risk factors, as sections of the retinal vein have been shown to have increased blood velocity and a propensity to develop arterialized endothelium.\textsuperscript{20,21}

Unlike other types of venous thrombosis, anticoagulation has not been shown to be effective in RVO. Meta-analysis of multiple trials found no obvious benefit to anticoagulation, antiplatelet agents, or thrombolytic agents.\textsuperscript{22,23} Treatment generally involves risk factor modification, with the use of local therapies including VEGF inhibitors, local steroid implants, or photocoagulation reserved for patients with vision loss, macular edema or neovascularization.\textsuperscript{19}

**UPPER EXTREMITY THROMBOSIS**

Thrombosis of the deep veins of the upper extremity (the brachial, axillary or cephalic veins) is far less common than lower extremity thrombosis, accounting for only 5\% of symptomatic cases, however upper extremity thrombosis accounts for approximately 50\% of hospital acquired thrombosis.\textsuperscript{24-26}
The vast majority of upper extremity thromboses, up to 80%, are provoked by the presence of an indwelling venous catheter. While symptomatic catheter associated thrombosis may be relatively uncommon, approximately 2% of patients with peripherally inserted central catheter lines develop symptomatic thrombosis, studies have shown that up to 66% of patients with venous catheters develop asymptomatic thrombosis that can be detected on screening ultrasound.

Unprovoked upper extremity thrombosis is exceedingly rare, occurring in only 2 per 100,000 patients per year. Unprovoked cases are often secondary to "effort" thrombosis, also known as Paget-Schroetter syndrome. More prevalent in younger patients, Paget-Schroetter syndrome is thought to be secondary to a combination of vessel micro trauma and local muscle hypertrophy from exercise that occur in patients predisposed to venous scarring or thoracic outlet syndrome.

A preceding history of strenuous upper extremity use or exercise is often noted. For catheter associated thrombosis current guidelines recommend keeping the catheter in place if it is needed as long as anticoagulation is initiated and continuing anticoagulation for 3 months after its removal. Given the high incidence of asymptomatic or minimally symptomatic thrombosis associated with peripherally inserted central catheters (PICCs), and the relatively low rates of pulmonary embolism (~5%), treatment with PICC removal alone may be a reasonable strategy.

For patients presenting with Paget-Schroetter syndrome with significant symptoms thrombolysis can be effective at reinstating vein patency, with success rates of 60-80%. Thoracic outlet decompression should be considered in young patients with Paget-Schroetter syndrome. Thrombolysis with venoplasty and first rib removal through an axillary or clavicular approach remain treatment options.
BUDD CHIARI SYNDROME (HEPATIC VEIN THROMBOSIS)

Thrombosis of the hepatic veins (Budd Chiari Syndrome) can result in significant morbidity including acute liver failure, encephalopathy, ascites, and portal hypertension. A minority of cases, approximately 20%, are asymptomatic at the time of detection. The diagnosis of Budd Chiari should be suspected in any patient with ascites and evidence of acute hepatic congestion.

Budd Chiari syndrome is a rare disorder, with scarce epidemiological data. One of the largest cohorts of 237 European and American patients found two-thirds were female with an average age of 35 years. MPNs are reported to be the cause of 40-50% of cases of primary Budd Chiari Syndrome. The JAK2V617F mutation can be detected in as many as 58% of patients with idiopathic Budd Chiari syndrome. Darwish Murad and colleagues examined a cohort of 163 patients with primary Budd Chiari syndrome and found that of those tested, the most common underlying etiologies were MPNs (49%), antiphospholipid syndrome (25%) and paroxysmal nocturnal hemoglobinuria (PNH) (19%). 23% had a systemic inflammatory disease including Behcet’s disease, inflammatory bowel disease, or other connective tissue disease. 38% of women in the cohort were on birth control or hormonal therapy, and 6% were recently pregnant. 21% of patients tested had an inherited thrombophilia. Budd Chiari syndrome can also present secondary to local disorders including malignancy, intrahepatic abscess or parasitic cysts, or trauma.

Anticoagulation should be initiated immediately in patients with Budd Chiari syndrome, with observational data suggesting this improves outcomes as the natural history of Budd Chiari syndrome is progressive liver failure and death. There are no randomized clinical trial data to guide management, but a step wise approach has been advocated for patients with progressive levels of liver failure which includes consideration of thrombolytic therapy, angioplasty/stenting, placement of a transjugular intrahepatic portosystemic shunt (TIPS), surgical shunting, or lastly, liver

This article is protected by copyright. All rights reserved.
transplantation.\textsuperscript{40,42} Modern series that incorporate the former treatment options report a 74% five year survival.\textsuperscript{36} In most cases anticoagulation should be continued indefinitely, even in asymptomatic patients, especially if an underlying thrombophilia is found.

**THROMBOSIS OF THE PORTAL VENOUS SYSTEM**

The hepatic portal vein, splenic vein, and mesenteric veins (some authors include the hepatic veins) comprise the hepatic portal venous system or “splanchnic veins.”\textsuperscript{43} Portal vein thrombosis is the most common form of splanchnic vein thrombosis accounting for 77% in a large prospective series of 604 patients, with 38% of patients having multiple splanchnic vein thromboses at presentation.\textsuperscript{44} Splanchnic vein thrombosis is a heterogeneous disease which limits the ability to make generalized recommendations about its treatment. Many factors including the provoking etiology, the level of symptoms (which can range from asymptomatic to highly symptomatic organ failure), the bleeding risk, and the risk of thrombus propagation should be taken into consideration when treating patients with splanchnic vein thrombosis. In general, anticoagulation is warranted for symptomatic cases, while guidelines recommend no anticoagulation or at least a careful risk/benefit analysis in patients with asymptomatic, incidentally found splanchnic vein thrombosis (not including Budd Chiari).\textsuperscript{32,45} With these generalities in mind, in the following sections, we outline specifics about each of the splanchnic veins.

**Portal Vein Thrombosis**

Partial or completely occlusive portal vein thrombosis (PVT) is often clinically silent, but rarely can be associated with significant symptoms including new onset or worsening portal hypertension, acute gastrointestinal bleeding, decompensation of previously stable cirrhosis, or intestinal ischemia.\textsuperscript{40,46}
Large studies of portal vein thrombosis have found a population prevalence of 1% on autopsy with the most common precipitants including cirrhosis (28%), primary hepatobiliary malignancy (23%), secondary malignancy (44%), idiopathic (14%), infectious or inflammatory abdominal processes (10%), and MPNs (3%).\textsuperscript{47} Portal vein thrombosis is also found after abdominal surgery, especially laparoscopic splenectomy with an incidence up to 5-10%, typically presenting with post-operative nausea, vomiting and abdomen pain.\textsuperscript{48}

Clinically, cirrhosis is one of the most commonly associated precipitants of PVT. In cirrhotic patients, rates of portal vein thrombosis have been reported in 5-27% of cases.\textsuperscript{49} The development of portal vein thrombosis in cirrhosis is likely a multifactorial process brought about by decreased portal blood flow, local inflammatory factors and clotting factor derangements inherent in cirrhosis which predispose to a prothrombotic state.\textsuperscript{50} The incidence of portal vein thrombosis has been shown to correlate with the degree of liver impairment, and occurs at different frequencies based on the etiology of cirrhosis.\textsuperscript{51,52} The natural history of portal vein thrombosis in cirrhotic patients is not well studied, and there is limited data on spontaneous recanalization or progression rates. A retrospective study of patients with viral associated cirrhosis found an incidence of 28% with a spontaneous regression rate of 47%, stable disease in 45%, and progression in 7%.\textsuperscript{53} Studies evaluating predictors of portal vein thrombosis in cirrhotic patients have shown that a portal flow rate <15 cm/sec is a significant risk factor for PVT development, and have also found that cirrhotic patients who develop PVT are more likely to have worse MELD scores, lower platelets, lower albumin and lower circulating levels of protein C, protein S and antithrombin III.\textsuperscript{53,54} Recently, a large prospective study of 1243 cirrhotic patients followed on screening ultrasounds confirmed that the severity of liver disease predicts PVT development, but did not find that the development of PVT worsened liver disease severity.\textsuperscript{55}
Idiopathic portal vein thrombosis often precedes the diagnosis of gastrointestinal or hematologic malignancy. One recent cohort study of 924 patients with portal vein thrombosis attempted to assess the risk of malignancy after extended follow up, finding 161 patients (17%) would ultimately be diagnosed with malignancy, of which 48 patients (5%) had malignancy of the liver, 19 (2%) had malignancy of the pancreas and 15 (1.6%) had MPNs.55

There are no randomized controlled trials evaluating anticoagulation in acute symptomatic PVT, however data suggests that early initiation of anticoagulation for acute PVT is associated with higher rates of recanalization. Recanalization rates as high as 90% have been reported in non-cirrhotics receiving anticoagulation, along with a reduction in recurrent thrombotic events and low rates of bleeding.56,57 A more recent meta-analysis of the use of anticoagulation with PVT found increased recanalization rates compared with patients who do not receive anticoagulants, with lower rates of variceal bleeding.58 Data on alternative treatment modalities including surgical thrombectomy, systemic or in situ thrombolysis, and TIPS is limited with evidence of increased peri-procedure related complications and mortality. Patients with post-surgical or other provoked thrombosis should be treated for 3 months while idiopathic PVT or those associated with severe thrombophilia such as MPNs require indefinite anticoagulation.

Treatment of chronic PVT is less straightforward, particularly in patients with cirrhosis. In patients with non-cirrhotic chronic portal vein thrombosis, prolonged anticoagulation therapy should be considered if the patient has irreversible thrombotic risk factors and no major contraindications, however guidelines are lacking on treating chronic cirrhotic PVT due to a paucity of data examining the risks and benefits of anticoagulation in this population. A reasonable approach is to anticoagulate cirrhotic patients who present with increasing symptoms. Liver transplant patients should also be considered for anticoagulation as recanalization of the portal vein can often increase
surgical options during transplantation of the liver. There are a small number of studies which have evaluated the use of anticoagulation in cirrhotic patients with chronic PVT, many of which suggest efficacy and safety, however large randomized trial data is lacking. Among select studies, recanalization rates approach 75% in the treatment arm, with progression rates as high as 71.4% in the observation arms; however, high rates of recurrence (38.5%) have been reported with discontinuation. Although studies suggest recanalization improves overall cirrhotic endpoints including portal hypertension related bleeding, ascites, and encephalopathy, these findings did not reach significance. Retrospective data from the national inpatient sample suggests that cirrhotic patients with a documented PVT had longer hospital length of stay, higher mean hospital charges, and a higher proportion of cirrhosis-related complications. One study evaluating prophylaxis to prevent PVT found that the group receiving anticoagulation had significantly less likelihood of developing a PVT, developing decompensated liver failure, and a significant survival benefit.

Bleeding complications have generally been low, although variceal bleed prophylaxis was not used consistently. At least one study noted significantly lower bleeding rates in the cirrhotic patients receiving anticoagulation compared to the control group. The ideal anticoagulant choice in cirrhosis is beyond the scope of this review, however our practice has been to use low molecular weight heparin or more recently direct oral anticoagulants (DOACs) in select patients.

**SPLENIC VEIN THROMBOSIS**

Isolated splenic vein thrombosis (SVT) is often secondary to pancreatic disorders including pancreatic cancer, pseudocysts, pancreatic abscess and especially pancreatitis, occurring in up to 22% of patients with acute pancreatitis, and 12% of patients with chronic pancreatitis. SVT often causes left sided or “sinistral” portal hypertension as collateral blood flows through the splenoportal and gastroepiploic systems leading to a confined venous hypertension and the development of gastric varices localized to the short gastric and left gastroepiploic veins. Sinistral portal hypertension significantly increased the risk of upper gastrointestinal bleeding which was a common
first presenting symptom of SVT before the routine use of CT scanning. Rates of gastric varices in SVT patients range from 53% - 77%, with reported rates of clinically significant gastrointestinal bleeding ranging from 4%-12%. Splenomegaly occurs in 42-54% of SVT patients.69 Sinistral portal hypertension can be cured with splenectomy which is the treatment of choice for patients with uncontrollable bleeding episodes.72 There is data to suggest that patients without objective evidence of gastrointestinal bleeding may be managed expectantly.72 No prospective trial has evaluated the safety and utility of anticoagulation in patients with SVT specifically. The safety of vitamin K antagonists was demonstrated in a large cohort of 375 patients with splanchnic vein thrombosis, 112 of which had splenic vein thrombosis. While data specific to splenic vein thrombosis was not reported, an acceptably low rate of major bleeding was found overall (1.2%).73 A second prospective study of anticoagulation in 102 patients with portal vein thrombosis including 41 patients with thrombosis extending into the splenic vein found a recanalization rate of 56%.74 Anticoagulation should be considered for splenic vein thrombosis especially acute thrombosis in the setting of surgery or pancreatitis. A short treatment course of 3 months may suffice. Splenectomy should be reserved for refractory patients with uncontrollable bleeding episodes, with laparoscopic splenectomy offering less morbidity.

MESENTERIC VEIN THROMBOSIS

While often clinically silent, approximately 5% of cases of acute mesenteric ischemia are caused by venous thrombosis.75 The superior mesenteric vein is more commonly involved, leading to impaired drainage from the distal small bowel provoking bowel wall edema and subsequent hemorrhagic infarction.76
Epidemiologic studies on mesenteric thrombosis are sorely lacking, but small studies have confirmed it to be a rare event, accounting for only 0.002-0.06% of all inpatient admissions.\(^7\)

While often presenting as an extension of other splanchnic vein thrombosis, there are no large studies examining the incidence of provoking conditions associated with isolated mesenteric vein thrombosis. One study of 51 patients presenting over a 6-year period to a single institution found a detectable associated condition in 80% of patients. 25% had a local process including pancreatitis, inflammatory bowel disease or recent surgery, 24% had a malignancy, 12% had venous congestion as defined by portal hypertension, severe heart failure or morbid obesity, and 29% were noted to have a previous or concurrent extra mesenteric thrombosis.\(^7\) Studies specific to patients with inflammatory bowel disorders have suggested a high inherent prevalence of mesenteric vein thrombosis (26%).\(^7\)

Of the splanchnic vein thromboses, isolated occult mesenteric vein thrombosis is the least likely to be associated with malignancy or MPNs. Søgaard and colleagues examined a data set containing 126 patients with occult mesenteric vein thrombosis and found only one associated malignancy and no associated MPNs.\(^8\) Other small series have noted about 25% of patients will have an associated intraabdominal malignancy.\(^7\) Small studies and case reports have suggested an increased incidence of inherited thrombophilia in patients with mesenteric vein thrombosis including activated protein C resistance, protein C and S deficiency, prothrombin gene mutation G20210A, factor V Leiden gene mutation, and antiphospholipid syndrome, however the clinical utility and changes in management that would arise from testing for these entities should be considered on a case by case basis.\(^8\)^\(^1\),\(^8\)^\(^2\)

Anticoagulation should be initiated immediately for both acute and subacute mesenteric vein thrombosis. For cases with significant symptoms, IV fluids, bowel rest, decompression, nutritional support and careful monitoring should be undertaken. Surgical interventions may be necessary in
patients who have complications of mesenteric ischemia which can include catheter directed thrombolysis, exploratory laparotomy with bowel resection as needed.\textsuperscript{83,84} Retrospective studies have suggested that rates of major bleeding in patients with mesenteric thrombosis on anticoagulation are low (2.6%).\textsuperscript{85} Despite modern treatment options, 30-day mortality for mesenteric vein thrombosis remains high at a reported 20%.\textsuperscript{86}

**RENAL VEIN THROMBOSIS**

Renal vein thrombosis (RVT) may be asymptomatic, but can present acutely, with symptoms including flank pain, hematuria, nausea, vomiting, anorexia, fever, and acute renal dysfunction.\textsuperscript{87,88} One large cohort study of 218 individuals diagnosed with first incident RVT found malignancy (66%) and nephrotic syndrome (20%) to be the most common underlying etiologies. Amongst these patients, the left renal vein was implicated more often than the right (43% vs. 33%), with bilateral renal vein involvement (21%) and progression to the inferior vena cava (43%) being fairly common.\textsuperscript{87} A large retrospective study of patients with nephrotic syndrome found a 1\% annual incidence of venous thromboembolism and a 1.5\% annual incidence of arterial thrombosis, with the highest incidence of thrombosis in membranous glomerulonephritis.\textsuperscript{89} Several potential thrombosis promoting mechanisms have been suggested in nephrotic syndrome, falling into two main categories; urinary loss of anti-thrombotic clotting factors, and a relative increase in prothrombotic factors.\textsuperscript{90,91} Nephrotic syndrome results in decreased circulating levels of antithrombin III, plasminogen and possibly proteins C and S.\textsuperscript{91,92} Several prothrombotic factors including factor V, factor VIII, Von Willebrand factor, fibrinogen and plasminogen activator inhibitor are also increased.\textsuperscript{92-94} Decreased osmotic pressure and hypoalbuminemia subsequently stimulates the synthesis of beta-thromboglobulin and fibrinogen in the liver, leading to increased platelet count and aggregation, increased blood viscosity, and promotion of erythrocyte aggregation.\textsuperscript{90,94}
There is debate about the use of prophylactic anticoagulation in nephrotic patients to prevent thrombosis, stemming from a lack of controlled prospective data. One prospective uncontrolled study of LMWH prophylaxis in 30 patients with nephrotic syndrome found no thrombosis on screening imaging after 12 months of therapy. For the asymptomatic patient with newly discovered chronic RVT, anticoagulation should be considered if there are no contraindications, with consideration for a longer duration of therapy if the patient remains nephrotic. Acute symptomatic RVT is treated with systemic anticoagulation which should be continued until the proteinuria resolves. Local thrombolytic therapy, with or without extraction catheter thrombectomy, has yielded acceptable results in patients requiring acute intervention, with surgical thrombectomy reserved only as a last resort for patients with acute bilateral renal vein thrombosis and renal failure.

CONCLUSION
Venous thrombosis in unusual sites has unique and obscure provoking factors, often requiring the physician to consider an individualized workup and treatment plan. For idiopathic cases of hepatic vein and splanchnic vein thrombosis the practitioner should consider work up of MPN, antiphospholipid syndrome, and flow cytometry for PNH while renal vein thrombosis heralds evaluation for nephrotic syndrome and malignancy. Anticoagulation is initiated for all venous sites except for retinal vein thrombosis and occasionally asymptomatic, incidentally found splanchnic vein thrombosis. Duration of anticoagulation is variable based on the site of thrombosis and resolution of the provoking etiology, but generally consists of 3-6 months, up to indefinite therapy. More studies are needed to evaluate the risks and benefits of anticoagulation in splanchnic vein thrombosis and prophylactic anticoagulation in nephrotic syndrome.
REFERENCES


This article is protected by copyright. All rights reserved.


<table>
<thead>
<tr>
<th>Common causes</th>
<th>Suggested workup</th>
<th>Management</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebral Vein</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen containing oral contraceptive pills</td>
<td>Appropriate neuroimaging</td>
<td>6 months of anticoagulation is generally sufficient as long as the provoking cause is removed/treated. Given low recurrence rates, even in unprovoked cases, 6 months is sufficient.</td>
<td>Recurrence rates are very low after removal of the provoking etiology, and even in unprovoked cases. Indefinite anticoagulation is usually reserved only for recurrent cases.</td>
</tr>
<tr>
<td>Pregnancy/postpartum</td>
<td>Screen for estrogen use/pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inherited/acquired thrombophilia</td>
<td>Thrombophilia screens are often considered, but do not change management.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local factors (cancer, trauma, abscess, meningitis, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Retinal Vein</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provoked by arterial risk factors:</td>
<td>Complete eye examination</td>
<td>No role for anticoagulation</td>
<td>Risk factors for retinal vein occlusion are similar to those seen in arterial disease. Anticoagulants should not be used and may worsen outcomes. Treatment is generally guided by ophthalmologists.</td>
</tr>
<tr>
<td>- Age,</td>
<td>Fundus examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- hypertension,</td>
<td>Visual acuity testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- diabetes,</td>
<td>Fluorescein angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- smoking,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- obesity,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hyperlipidemia.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Also rarely, severe glaucoma or retinal arterial abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Upper extremity</strong></td>
<td>Catheter associated: None</td>
<td>Catheter associated:</td>
<td></td>
</tr>
<tr>
<td>Indwelling venous lines.</td>
<td>May keep catheter in if needed. Treat with anticoagulation for 3 months.</td>
<td></td>
<td>Many PICC catheter associated thrombosis can likely be treated with catheter removal alone.</td>
</tr>
<tr>
<td>Paget-Schroetter syndrome.</td>
<td>Idiopathic: Consider referral to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter associated: None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic: Consider referral to</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prothrombin gene G20210A is a commonly associated thrombophilia.
<table>
<thead>
<tr>
<th>Common causes</th>
<th>Suggested workup</th>
<th>Management</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>vascular surgery for thrombolysis, and consideration of thoracic outlet decompression if evidence of venous thoracic outlet syndrome.</td>
<td>months post catheter removal.</td>
<td>Idiopathic: initiate anticoagulation and consider refer to vascular surgery for consideration of thrombolysis and thoracic outlet decompression</td>
</tr>
<tr>
<td>Local factors (Trauma, infection, axillary cancer)</td>
<td>Doppler ultrasonography</td>
<td>Acute treatments:</td>
<td>Anticoagulation is generally given indefinitely unless a resolvable provoking risk factor is present.</td>
</tr>
<tr>
<td>Myeloproliferative disorder</td>
<td>CT of the liver</td>
<td>• Anticoagulation</td>
<td></td>
</tr>
<tr>
<td>Estrogen use/pregnancy</td>
<td>Venography</td>
<td>• Consider systemic or catheter directed thrombolysis/venoplasty.</td>
<td></td>
</tr>
<tr>
<td>PNH</td>
<td></td>
<td>• TIPS if refractory</td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid syndrome.</td>
<td></td>
<td>• Liver transplant if failure eminent.</td>
<td></td>
</tr>
<tr>
<td>Inflammatory syndromes: Behçet's, etc.</td>
<td></td>
<td>Treatment of the underlying cause if identified.</td>
<td></td>
</tr>
<tr>
<td>Local factors (Cancer, hepatic abscess, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Membranous webs of the IVC/Hepatic veins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Vein (Budd Chiari)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JAK2V617F mutation (MPN workup)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow cytometry for PNH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen for estrogen use/pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta2 glycoprotein IgG, IgM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticardiolipin  IgG, IgM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consideration of systemic inflammatory syndromes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common causes</td>
<td>Suggested workup</td>
<td>Management</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------</td>
<td>------------</td>
<td>----------</td>
</tr>
<tr>
<td><strong>Splanchnic Vein</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In general</td>
<td>CT scan of the abdomen</td>
<td>For asymptomatic incidentally found cases in the setting if cirrhosis, recent surgery, or known abdominal pathology: The natural history is not well defined, especially in cases of chronic thrombosis. Many do not treat which is consistent with some major guidelines. If treatment is offered, reimaging in 3 months to assess for recanalization.</td>
<td>Prospective data on treatment is lacking. Asymptomatic incidentally found cases with obvious causes can often be observed. Anticoagulation should be initiated for symptomatic cases.</td>
</tr>
<tr>
<td>• Cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Post abdominal surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Abdominal infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• MPN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vein specific common causes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Portal Vein</strong></td>
<td></td>
<td>For symptomatic cases: Initiate anticoagulation and treat the underlying cause. Treat for at least 3 months if a resolvable provoking etiology is present.</td>
<td></td>
</tr>
<tr>
<td>• Cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hepatobiliary cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Splenic Vein</strong></td>
<td></td>
<td>Splenic vein thrombosis leading to sinistral portal hypertension with significant bleeding can be treated with splenectomy.</td>
<td></td>
</tr>
<tr>
<td>• Pancretatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pancreatic cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pancreatic pseudo cyst/abscess</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mesenteric Vein</strong></td>
<td></td>
<td>For splanchic vein thrombosis leading to mesenteric ischemia, catheter directed thrombolysis or surgical intervention should be</td>
<td></td>
</tr>
<tr>
<td>• Postoperative or malignancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Inflammatory bowel disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common causes</td>
<td>Suggested workup</td>
<td>Management</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Renal Vein</td>
<td>Malignancy</td>
<td>CT scan of the abdomen</td>
<td>Initiate anticoagulation. For cases associated with nephrotic syndrome initiate appropriate treatment and continue anticoagulation for a minimum of 3 months until proteinuria has resolved.</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
<td>Urinalysis</td>
<td>Local thrombolysis/surgery for severe cases leading to organ dysfunction.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 hour urine protein.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum albumin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider renal biopsy if appropriate.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MPN, Myeloproliferative neoplasm; PNH, Paroxysmal nocturnal hemoglobinuria; TIPS, Transjugular Intrahepatic Portosystemic Shunt; PICC, Peripherally inserted central catheter