bjh guideline

Guidelines on the investigation and management of venous thrombosis at unusual sites

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Deep vein thrombosis (DVT) of the lower limb veins and pulmonary embolism (PE) are the most commonly encountered manifestations of venous thrombosis in routine clinical practice. Consequently, they have a strong evidence base supporting their optimal management. Venous thrombosis at other 'unusual sites' is well documented, but given the paucity of robust studies its management has often been extrapolated from experience of lower limb DVT and PE. The objective of this guideline is to provide healthcare professionals with guidance, based on contemporary evidence, on the appropriate investigation and treatment of venous thrombosis at these other sites.

The writing group was selected to be representative of UK-based experts. MEDLINE and EMBASE were searched for publications from 1996 onwards using the key word relevant to the venous thrombosis site and limits clinical trial, humans, core clinical journals, and English language. Additional relevant papers were identified by screening reference lists and by the identification of publications known to the writing group. The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology (BCSH). The guideline was then reviewed by a sounding board of approximately 50 UK haematologists, the BCSH and the British Society for Haematology (BSH) Committee and comments incorporated where appropriate. The 'GRADE' system was used to quote levels and grades of evidence, details of which can be found at http://www.bcshguidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION/43_GRADE.html.

Where evidence exists, the relevance of hereditary thrombophilia to the development and subsequent management of thrombosis at specific unusual sites is discussed. If unusual site thrombosis develops in the context of an antiphospholipid syndrome, the risk of recurrence is felt to be increased and long-term anticoagulation should be considered.

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Cerebral venous and sinus thrombosis

The epidemiology, diagnosis and management of cerebral venous and sinus thrombosis (CVST) have been reviewed in consensus statements published in 2010 and 2011 (Einhaupl *et al*, 2010; Saposnik *et al*, 2011). CVST, responsible for less than 1% of all strokes, most often affects young adults and children with approximately 75% of patients being female (Stam, 2005). Reported annual incidence rates include 4 per million of the population, 7 per million children and about 12 per million deliveries.

Obstruction of cerebral veins causes cerebral oedema and venous infarction, while occlusion of venous sinuses causes intracranial hypertension. Therefore, CVST should be considered in young and middle-aged patients with recent unusual headache, stroke-like symptoms in the absence of usual risk factors, intracranial hypertension or haemorrhagic cerebral infarcts. The most sensitive diagnostic test is magnetic resonance venography [magnetic resonance imaging (MRI) with venography]. If MRI is not available then high resolution computed tomography (CT) as an initial examination is useful but it can be normal initially.

Recognized underlying causes include infection, particularly of the head and neck, systemic inflammatory disorders, leukaemia (especially with asparaginase treatment), head injury and dehydration. While myeloproliferative neoplasms (MPNs), such as polycythaemia vera and essential thrombocythaemia, are causes of CVST (De Stefano *et al*, 2008), in the absence of overt MPN the *JAK2* mutation has not been associated with CVST (Koopman *et al*, 2009). Use of oestrogen-containing combined oral contraceptives (C-OCPs) is a precipitating factor (de Bruijn *et al*, 1998a; Martinelli *et al*,

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1998a) with a higher risk associated with third generation pills (de Bruijn *et al*, 1998b). A systematic review of 17 studies found an increased risk of CVST in patients using C-OCPs [odds ratio (OR) 5·6; 95% confidence interval (CI) 4·0–7·9], in patients with *F5* R506Q (factor V Leiden; OR 3·4; 95% CI 2·3–5·1), with *F2* G20210A (prothrombin gene mutation; OR 9·3; 95% CI 5·9–14·7) and with high fasting levels of homocysteine (OR 4·1; 95% CI 2·5–6·5) (Dentali *et al*, 2006a). There were insufficient patients with deficiency of antithrombin, protein C or S to draw conclusions.

Although the prognosis of CVST is generally good, death may occur within hours of presentation due to cerebral herniation. Coma at presentation, thrombosis of the deep cerebral venous system, CNS infection, cancer and intracranial haemorrhage (ICH) are associated with a worse prognosis (Ferro *et al*, 2004; Wasay *et al*, 2008). Mortality in the first month is 5·6% with 70% of deaths directly attributable to the CVST (Dentali *et al*, 2006b). Most subsequent deaths are due to cancer. Eighty percent of surviving patients recover completely or have only a mild functional or cognitive deficit (Dentali *et al*, 2006b). Recanalization usually occurs in the first 4 months irrespective of continued anticoagulation (Baumgartner *et al*, 2003; Dentali *et al*, 2006b).

An updated systematic review of therapeutic dose unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) and the use of thrombolysis was undertaken in 2010 (Einhaupl *et al*, 2010). Anticoagulant therapy was associated with a pooled relative risk of death of 0·33 (95% CI 0·08–1·21) and of death or dependency of 0·46 (95% CI 0·16–1·31), based on two small studies. No new symptomatic intracerebral haemorrhages were observed in patients treated with heparin. Given that early treatment is likely to be safe and potentially beneficial it is recommended that patients with CVST without contraindications to anticoagulant therapy should be treated with therapeutic dose heparin. ICH is not regarded as a contraindication to anticoagulant treatment.

If patients deteriorate despite adequate heparin therapy and other causes of deterioration have been excluded, thrombolysis may be a therapeutic option in selected cases. However, a small non-randomized study of localized thrombolysis demonstrated that patients with large haemorrhagic infarcts and impending herniation did not benefit (Stam *et al*, 2008). An expert consensus concluded that thrombolytic therapy should be reserved for patients with extensive CVST that is likely to be fatal or not responding to anticoagulant therapy but is not indicated when deterioration is caused primarily by ICH (Ageno *et al*, 2010a). In patients with impending herniation surgical decompression should be considered.

The optimal duration of anticoagulation is unknown. Indeed, observational studies are unclear as to whether anticoagulation reduces the risk of recurrent CVST (Kenet *et al*, 2007). Expert consensus recommended 7–14 d heparin treatment to ensure consistent therapeutic anticoagulation (Ageno *et al*, 2010a). This could be followed by a vitamin K antagonist for 3 months if CVST was secondary to a transient risk factor, for 6–12 months in patients with unprovoked CVST and in those with 'mild' thrombophilia, such as heterozygous *F5* R506Q or *F2* G20210A mutation (Einhaupl *et al*, 2010). Long term anticoagulation has been suggested for patients with recurrent episodes of CVST and in those with one episode of CVST and 'severe' thrombophilia, such as antithrombin, protein C or protein S deficiency, homozygous *F5* R506Q or *F2* G20210A mutation, antiphospholipid antibodies and combined abnormalities (Einhaupl *et al*, 2010). An alternative expert consensus suggested that indications for continued anticoagulation in patients with unprovoked CVST were incomplete clot resolution on repeat imaging, persisting risk factors or thrombophilia (Ageno *et al*, 2010a).

A systematic review identified an overall CVST recurrence rate of only 2·8% (Dentali *et al*, 2006b). In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) the CVST recurrence rate was 1·5% per annum with a 3 year cumulative recurrence of 5·7% (Miranda *et al*, 2010). An increased risk of recurrence was associated with male sex [Hazard Ratio (HR) 6·2, 95% CI 2·1–18·6]. This was not completely explained by a lower risk of recurrence in women with a first episode of C-OCP-associated CVST. These observational studies also demonstrated subsequent DVT or PE in 3–4% of CVST patients, with male sex and MPN being prominent risk factors (Miranda *et al*, 2010). The risk of recurrent CVST in pregnancy appears to be low (Dentali *et al*, 2006b) but whether there is a need for thromboprophylaxis in pregnancy is unknown. In children with CVST, recurrence only occurred when CVST was diagnosed after 2 years of age and was more likely when there was persistent occlusion on repeat imaging and in association with *F2* G20210A (Kenet *et al*, 2007).

Recommendations

1 It is suggested that patients with CVST without contraindications to anticoagulant therapy should be treated early with therapeutic dose LMWH for at least 7 d (2C).

2 The presence of intracranial haemorrhage, in association with CVST, should not be regarded as a contraindication to anticoagulation (1C).

3 It is suggested that thrombolytic therapy should be reserved for patients with extensive CVST that is likely to be fatal or is not responding to anticoagulant therapy. It is not indicated when deterioration is caused primarily by ICH (2C).

4 Surgical decompression should be considered in patients with impending herniation (2C).

5 It is suggested that oral anticoagulation with warfarin should be delayed until the patient's condition has stabilized (2C). It is suggested that a minimum of 3 months treatment is given (2C).

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6 It is suggested that consideration is given to continuing anticoagulation in patients with persisting risk factors, and in those with unprovoked CVST or persistent venous occlusion on repeat imaging (2C). Testing for heritable thrombophilia has uncertain predictive value for recurrence of CVST. However, continued anticoagulation in patients with antithrombin, protein C or protein S deficiency is suggested by some experts (2C).
7 Acquired risks should be removed or minimized to prevent recurrence, e.g. C-OCP, hormone replacement therapy (HRT) exposure or obesity (1C).

Retinal vein occlusion

In populations over the age of 40 years the annual incidence of retinal vein occlusion (RVO) is 1·6/1000 of which 75% are branch retinal vein occlusion (BRVO) and 25% central retinal vein occlusion (CRVO) (Klein *et al*, 2000; Cugati *et al*, 2006). The incidence rises to approximately 5/1000/year over the age of 64 years (David *et al*, 1988). Typical presentation is with acute, painless visual loss in one eye. The diagnosis can usually be made by clinical examination alone.

In a meta-analysis of 21 studies, hypertension was found in 64% of cases, hyperlipidaemia in 35% and diabetes in 15%. RVO is predominantly a disorder of the elderly but is not associated with direct measures of atherosclerosis, endothelial dysfunction, inflammation or coagulation activation. Open-angle glaucoma and raised intraocular pressure are local risk factors for CRVO. There is no strong association with hereditary thrombophilia: a meta-analysis of 26 studies found that only hyperhomocysteinaemia (OR 8·9 95% CI 5·7–13·7) and anticardiolipin antibodies (OR 3·9 95% CI 2·3–6·7) had significant associations with RVO (Hayreh *et al*, 1994). The association with *F5* R506Q was of borderline significance (OR 1·5 95% CI 1·0–2·2) (Janssen *et al*, 2005).

The visual prognosis is driven by the development of macular oedema and neovascularization rather than recurrence. Consequently, standard therapy has been laser photocoagulation. Intraocular steroids are licensed for macular oedema as are anti-angiogenic agents (ranibizumab, bevacuzimab), which have also produced improved visual outcomes [e.g. clinically significant improvement in 46% vs. 17% in control subjects (Brown *et al*, 2010)].

Ipsilateral recurrence rate is estimated at 1% per annum with a future 10–15% risk of contralateral RVO. The role of anticoagulant therapy in preventing recurrence is unknown and trial data limited. Trials of antiplatelet therapy have failed to show significant benefit (Houtsmuller *et al*, 1984). Moreover, a large cohort study of 686 patients with RVO showed that those taking antiplatelet agents or anticoagulation at the time of occlusion had more severe retinal haemorrhage and were more likely to show subsequent deterioration in vision (Hayreh *et al*, 2011). Two randomized trials of LMWH (6 months and 20 d) both resulted in improved visual outcome compared to aspirin. LMWH was not associated with an excess of bleeding but there were trends towards reduced neovascularization and reduced recurrence (Farahvash *et al*, 2008; Ageno *et al*, 2010b). However, because the visual benefit may arise from an anti-angiogenic effect of heparin and because comparison was with aspirin, which is not recommended, this should not be extrapolated to support anticoagulation in general. While aspirin is not recommended in treatment or secondary prevention of RVO, in patients with underlying cardiovascular disease an anti-platelet agent should be considered for secondary prophylaxis for atherosclerosis. Early trials of thrombolytic therapy were complicated by haemorrhage but a more recent randomized trial of low dose tissue plasminogen activator followed by 8 d of heparin showed benefit at 1 year, compared to haemodilution, for CRVO but not BRVO without any major haemorrhages (Hattenbach *et al*, 2009). None of these interventions, including haemodilution (Chen *et al*, 1998), have accumulated sufficient supporting evidence to become the standard of care. Ophthalmology guidelines (http://www.rcophth.ac.uk/page.asp?section=451&sectionTitle=Clinical+Guidelines) and expert opinion (Hayreh *et al*, 2002, 2011) do not recommend routine thrombophilia testing or antiplatelet or anticoagulation therapy. However, LMWH has received cautious support from the results of a meta-analysis (Lazo-Langner *et al*, 2010).

Recommendation

1 Patients with CRVO and BRVO should be assessed for coexistent risk factors, such as hypertension and glaucoma, which should be managed accordingly (1C).
2 Patients with RVO do not require investigation for thrombophilia (1B).
3 Patients with acute CRVO should be considered for treatment with LMWH for 1–6 months (2B).
4 Routine therapy with warfarin or anti-platelet agents is not recommended (2C).

Upper extremity venous thrombosis

Axillary, subclavian and brachial vein thrombosis

Upper extremity deep vein thromboses (UEDVT) may involve the axillary, subclavian and brachial veins. These account for up to 10% of all DVTs (Flinterman *et al*, 2008), and occur with a rate of around 16 per 100 000 of the population per annum (Spencer *et al*, 2007). UEDVT are considered primary if they are idiopathic or associated with thoracic outlet syndrome (TOS) or effort (Paget-Schroetter syndrome) (Paget, 1875; Von-Schroetter, 1884) or secondary if they are associated with an underlying precipitant such as placement of a central venous catheter.

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Thoracic outlet syndrome comprises compression of the neurovascular bundle in the thoracic outlet. The compression may be due to either boney structures, such as the first rib and clavicle, or muscle bulk. Paget–Schroetter syndrome is considered a form of TOS in which thrombosis is induced by microtrauma to the vessel after vigorous effort.

Central venous catheters (CVC), active malignancy, and inherited and acquired thrombophilia are considered risk factors for UEDVT. The most frequent risk factor is presence of a CVC (Spencer *et al*, 2007). Pacemakers are also a recognized risk factor for UEDVT. The incidence of UEDVT is highest for large diameter chest catheters (Grove & Pevec, 2000) and pacemakers with a higher number of leads (Rozmus *et al*, 2005; Korkeila *et al*, 2007). Upper limb surgery and plaster cast immobilization are associated with a 13-fold and sevenfold relative risk for UEDVT, respectively (Blom *et al*, 2005). Use of the C-OCP and HRT have not been shown convincingly to be risk factors. *F5* R506Q and the *F2* G20210A mutation may be risk factors for UEDVT but *F5* R506Q was found much less commonly in patients with idiopathic UEDVT compared with idiopathic lower limb DVT (12% vs. 30%, $P = 0{\cdot}009$) (Lechner *et al*, 2008).

A systematic review of poor methodological quality studies concluded that compression ultrasound with a sensitivity of 97% (95% CI, 90–100%) may be an acceptable alternative to venography in the investigation of suspected UEDVT (Di Nisio *et al*, 2010). The use of clinical decision rules combined with D-dimer testing for the exclusion of UEDVT has not been adequately assessed (Merminod *et al*, 2006).

The data on complication rates for UEDVT are derived from heterogeneous cohorts of patients. Pulmonary embolism (up to 30%), post-thrombotic syndrome (7–44%) (Hingorani *et al*, 1997; Prandoni *et al*, 2004; Kahn *et al*, 2005) and annual recurrence rates of 2–8% are reported (Prandoni *et al*, 1997, 2004; Baarslag *et al*, 2004; Martinelli *et al*, 2004). In a direct comparison of outcomes in patients with idiopathic UEDVT and lower extremity DVT, 5-year recurrence rates of 2% (95% CI 0–6) and 19% (16–22) respectively were described (Lechner *et al*, 2008).

A Cochrane analysis showed no benefit for prophylactic dose heparin or low dose vitamin K antagonists (VKA) on the prevention of death or symptomatic DVT in patients with CVCs (Akl *et al*, 2011). Low dose VKA therapy resulted in a significant reduction in asymptomatic DVT [RR 0·42 (0·28–0·61)] (Akl *et al*, 2011). There are no randomized controlled trials on the optimal treatment of patients with UEDVT. The majority of patients are managed with a combination of brief heparin therapy followed by a vitamin K antagonist for between 3 and 6 months. A retrospective analysis of 110 episodes of first rib resection and scalanectomy performed for management of TOS demonstrated no benefit for pre-operative endovascular intervention (thrombolysis +/− venoplasty) compared with anticoagulation alone (Guzzo *et al*, 2010).

Recommendations

1 Imaging investigation of suspected UEDVT should be by venography or compression ultrasound (1B).
2 Patients with CVCs should not routinely be treated with prophylactic heparin or low dose VKA for the prevention of venous thrombosis (1B).
3 Patients with TOS undergoing surgical decompression should not routinely receive thrombolytic therapy or venoplasty prior to the procedure (2B).
4 Patients with UEDVT should receive anticoagulation with heparin for at least 5 d and warfarin. The optimal duration of warfarin therapy is unknown. Periods of 3 to 6 months are associated with low risk of recurrence and are likely to be satisfactory (2B).

Jugular vein thrombosis

Jugular vein thrombosis is most commonly seen in association with local sepsis, inflammation or trauma. It is most often recognized as part of Lemierre syndrome, which is characterized by a history of recent oropharyngeal infection, clinical or radiological evidence of internal jugular vein thrombosis, and isolation of anaerobic pathogens, mainly *Fusobacterium necrophorum*. There appears to be an excess of jugular vein thrombosis in patients with ovarian hyperstimulation syndrome (Arya *et al*, 2001). Data on imaging and treatment are limited.

Recommendation

1 In the absence of specific studies, anticoagulation as for UEDVT should be considered (2C).

Vena caval thrombosis

Superior vena cava thrombosis

Obstruction of the superior vena cava (SVC) can be caused by malignant or benign disease. Malignancy is the commonest cause of SVC thrombosis accounting for up to 60% cases (Rice *et al*, 2006). Non-malignant causes are frequently due to indwelling central venous access devices or to pacemaker wires (Rice *et al*, 2006). Other recognized causes include infection and mediastinal fibrosis (Rizvi *et al*, 2008).

The most frequent presenting signs and symptoms of SVC thrombosis are face or neck swelling, upper limb swelling, dyspnoea, cough and dilated chest vein collaterals (Rice *et al*, 2006). The prevalence rate is unclear. However in the USA it is reported in 1–3% of cases of central venous access devices and 0·2–3·3% of cases of implanted pacemakers (Houmard *et al*, 1991; Barakat *et al*, 2000; Rice *et al*, 2006). CT scanning is the first imaging usually performed and contrast venography is performed if endovascular intervention is planned.

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All patients should receive anticoagulant therapy to reduce the risk of pulmonary emboli. In patients with severe symptoms due to benign SVC thrombosis, endovascular surgery with angioplasty and stenting is now considered to be first-line therapy (Rizvi *et al*, 2008). In cases of SVC thrombosis associated with malignancy, radiotherapy (along with chemotherapy if appropriate) may provide relief of symptoms. Anticoagulation, influenced by persisting risk factors, will often be continued long-term in patients with SVC thrombosis. The prognosis of SVC thrombosis is very much dependent upon the causes of the thrombosis. In cases of SVC thrombosis due to infection the prognosis is good because most cases respond to appropriate antibiotic therapy.

Recommendation

1 Patients with SVC thrombosis should receive anticoagulant therapy as for DVT (1C).
2 Endovascular surgery with angioplasty and stenting should be considered in patients with non-malignant SVC thrombosis with severe symptoms (1B).
3 Continued anticoagulation should be considered in patients with persisting risk factors (2C).

Inferior vena cava thrombosis

The aetiology of inferior vena cava thrombosis (IVCT) mirrors that of DVT. Malignancy, particularly renal cell carcinoma and other tumours close to the IVC, may cause IVCT either through direct invasion of the IVC or by compression. Non-malignant risk factors include congenital anomaly of the IVC, or external compression that leads to venous stasis and turbulent blood flow. Most cases of IVCT will present with signs and symptoms of a lower limb DVT or pulmonary embolism. Patients presenting with bilateral lower limb DVTs should have their IVC imaged. In the MAISTHRO (MAin-ISar-THROmbosis) registry of 1770 venous thromboembolism (VTE) patients, 53 (3·0%) had IVCT and of these 66% occurred in women and 74% under the age of 45 years (Linnemann *et al*, 2008). The infra-renal segment of the IVC is affected in >90%.

In the MAISTHRO VTE registry, a lupus anticoagulant was found in 10·9% of patients but inherited prothrombotic abnormalities did not appear more prevalent in patients with IVCT than in age-sex matched controls with lower limb DVT (Linnemann *et al*, 2008). There is an increased risk of IVCT associated with the use certain types of IVC filter (e.g. opposed biconical design) (Linnemann *et al*, 2008).

There are no data that suggest patients with IVCT should be managed differently from those with proximal lower limb DVT, however there may be a lower threshold for use of catheter-directed thrombolysis in cases with a low risk of haemorrhage. The optimal duration of anticoagulation is unclear although the natural history of IVCT is not to recanalize and for collateral circulation to develop, particularly in children, and therefore indefinite anticoagulation may be considered (Linnemann *et al*, 2008). The use of IVC filters and endovascular surgery is increasingly common.

Recommendation

1 Patients presenting with bilateral lower limb DVT should have their IVC imaged to exclude IVC thrombosis (1B).
2 Patients with acute IVCT should be considered for catheter-directed thrombolytic therapy or endovascular surgery (2C).
3 Duration of anticoagulation therapy should be based on the presence of persisting risk factors and degree of recanalization (2C).

Abdominal vein thrombosis

Portal vein thrombosis

The portal vein is formed from the superior mesenteric and splenic veins. The most common underlying aetiology of portal vein thrombosis (PVT) is cirrhosis (Valla *et al*, 2002). Other causes are intra-abdominal infection, inflammation or malignancy and blunt trauma or surgery. MPNs account for up to a quarter of cases (De Stefano *et al*, 1997) and PVT is a common presenting manifestation of MPN (Hoekstra *et al* 2011). Therefore all PVT patients should be assessed for the *JAK2* V617F mutation (Colaizzo *et al*, 2007; Austin & Lambert, 2008; Xavier *et al*, 2010). Paroxysmal nocturnal haemoglobinuria (PNH) is an important cause of intra-abdominal thrombosis (Ziakas *et al*, 2007). Heritable thrombophilias are an aetiological factor (Denninger *et al*, 2000; Janssen *et al*, 2000; Dentali *et al*, 2008) as may be antiphospholipid antibodies (Uthman & Khamashta, 2007).

Presentation can be acute with abdominal pain, fever and nausea, or chronic with symptoms of portal hypertension (variceal bleeding, ascites, hypersplenism). The diagnosis can be made by CT, MRI or Doppler ultrasound. The latter is simplest and has a 98% negative predictive value (Parikh *et al*, 2010).

The risk of anticoagulation-related bleeding is high in patients with cirrhosis presenting with acute or chronic PVT and anticoagulation is not usually given. In acute PVT without cirrhosis, anticoagulation with LMWH followed by warfarin is usually given, but decisions should be made on a case-by-case basis. There is no evidence to guide duration of anticoagulation. Although it has been suggested that anticoagulation should be given long-term in the presence of a heritable thrombophilia or if there is a failure of recanalization, this is not based on any strong evidence (Webster *et al*, 2005; Sarin *et al*, 2006; Amitrano *et al*, 2007; Parikh *et al*, 2010). Following PVT in patients with a MPN, recurrent thrombosis is relatively common (27–33%) (Hoekstra *et al*,

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2011) and there is stronger evidence for long-term anticoagulation. In this situation recurrence may be best prevented by a combination of both anti-platelet and oral anticoagulant agents (Hoekstra *et al*, 2011). In chronic PVT without cirrhosis there are no trials as to the usefulness of anticoagulation. It has been recommended that those without portal hypertension and with hypercoagulable states should be anticoagulated (Parikh *et al*, 2010) but, again, with no evidence.

Hepatic vein thrombosis

Hepatic vein thrombosis occurs in approximately 1–2 per million people per year. The usual presentation is with abdominal pain, ascites and hepatomegaly (Budd-Chiari syndrome). Many have an underlying prothrombotic disorder and up to half may have a MPN (Darwish Murad *et al*, 2009), with 30% of patients *JAK2* positive in this study. The diagnosis can be made with Doppler ultrasound, CT or MRI. Most patients are anticoagulated, and is followed by transjugular intrahepatic portal systemic shunting (TIPSS) in one third of cases (Darwish Murad *et al*, 2009). If this fails then liver transplantation should be considered. Use of thrombolysis has been reported in small case series only. This appears to be more effective when administered locally rather than systemically (Sharma *et al*, 2004).

Mesenteric vein thrombosis

Mesenteric vein thrombosis (MVT) accounts for 10% of mesenteric ischaemia (Grendell & Ockner, 1982). The most common causes are prothrombotic states, cancer, intra-abdominal inflammation or infection, cirrhosis and surgery (Kumar *et al*, 2001). When ischaemia is restricted to the mucosa the patient will present with abdominal pain and diarrhoea; transmural ischaemia leads to necrosis and peritonitis. CT or MRI is the diagnostic investigation of choice for suspected cases. Surgery is required in patients with peritonitis but otherwise anticoagulation is the treatment of choice (Bergqvist & Svensson, 2010). As for PVT, long-term anticoagulation has been proposed for patients with thrombophilia but this is not based on any evidence.

Splenic vein thrombosis

Isolated splenic vein thrombosis is rare and pancreatic disease is the most common aetiology (Sakorafas *et al*, 2000). It can present with variceal bleeding and splenomegaly but normal liver function (Koklu *et al*, 2004). Splenectomy is recommended for those with variceal bleeding (Zadrozny, 1999)

Recommendation

1 MPNs are a common cause of abdominal vein thrombosis and the *JAK2* mutation should be sought (1A).
2 PNH should be considered as a possible underlying diagnosis (1B).
3 Long term anticoagulation should be considered for abdominal vein thrombosis occurring in the presence of PNH or an MPN (2C).
4 Heritable thrombophilias may play a role in abdominal vein thrombosis but there is no evidence that their presence should alter management (2C).
5 In acute PVT without cirrhosis anticoagulation is recommended (1C) but there is no evidence as to whether it should be given for 3–6 months or long-term.
6 In PVT with cirrhosis the risk of anticoagulation will usually outweigh the benefit but an individual decision is needed for each patient (2C).
7 Acute hepatic vein thrombosis should be managed by anticoagulation and if required TIPSS (1B).
8 Patients with acute MVT without peritonitis can be managed conservatively with anticoagulation (1B). There is no evidence as to whether this should be given for 3–6 months or long-term.

Genito-urinary venous thrombosis

Renal vein thrombosis

Renal vein thrombosis (RVT) is an uncommon condition with a variable clinical presentation. Acute onset RVT usually affects neonates and infants in association with other illnesses and dehydration. Male children are affected twice as often as females and the left renal vein is affected twice as frequently as the right. Left-sided RVT may lead to gonadal vein thrombosis with painful swelling of the left testis and varicocele formation. In adults RVT is again more common in men than in women. Most cases of RVT in adults present with flank/loin pain and macroscopic haematuria (Wysokinski *et al*, 2008), which can be severe in the acute onset of thrombosis. In cases of bilateral RVT, individuals may present in acute renal failure.

Although RVT has numerous aetiologies, in the Mayo Clinic series of 218 patients with RVT (Wysokinski *et al*, 2008), 66·2% of patients had active cancer, 19·7% nephrotic syndrome, 14·4% infection and 11·9% cases were idiopathic. RVT has been identified prospectively in 22% cases of nephrotic syndrome (Llach *et al*, 1980) and has been associated with urological surgery, primarily renal transplantation (Asghar *et al*, 2007; Wysokinski *et al*, 2008). There are no clear associations between RVT and thrombophilia. RVT is classically diagnosed by CT scanning with simultaneous intravenous administration of contrast media, although selective renal venography may be regarded as the definitive test.

The management of patients with RVT should reflect the underlying causative factors. Anticoagulation with heparin and subsequently warfarin is common but there is little evidence to guide the duration of treatment. The prognosis of RVT depends upon multiple factors, with normal baseline

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renal function at presentation being associated with a favourable outcome. In cases of malignancy-associated RVT, the prognosis is poor with a median survival of 17·8 months (Wysokinski *et al*, 2008). Conversely, RVT associated with nephrotic syndrome is not associated with an increased risk of mortality. Recurrent RVT is uncommon.

Recommendation

1 Investigation of patients with RVT for underlying thrombophilia is not routinely indicated, and should follow existing guideline criteria (2C).
2 Decisions as to the use of anticoagulant therapy should take into account the aetiology of the RVT and the risk of anticoagulant-associated haemorrhage (2C).

Ovarian vein thrombosis

Ovarian vein thrombosis complicates 1/600 to 1/2000 pregnancies (Khlifi *et al*, 2010). It usually presents within 4 weeks of delivery and most commonly in the first 4 d. Symptoms are vague and include lower abdominal pain, tenderness, pyrexia and tachycardia. It can be difficult to distinguish from other pelvic infective or inflammatory disorders. Right-sided cases predominate (80–90%) (Khlifi *et al*, 2010). Diagnosis is best achieved with CT or MRI scanning. Ovarian vein thrombosis may extend into the renal veins and IVC and, in 13–33% of cases, embolize with 4% proving fatal (Al-toma *et al*, 2003). Most cases follow delivery but cases have been described after post-abortion infection, pelvic inflammatory disease and recent pelvic surgery complicated by infection. Treatment is with conventional anticoagulation.

In contrast to the rarity and life-threatening potential of post-partum ovarian vein thrombosis, it is frequently detected incidentally in patients who have undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy with retroperitoneal lymph node dissection (Yassa & Ryst, 1999). In a series of 50 patients who underwent this type of surgery for cancer, all had CT scans preoperatively which showed no thrombosis but on the routine post-operative CT scans performed 3–20 months later, 40 (80%) had unilateral ovarian vein thrombosis (75% right-sided). All of these ovarian vein thromboses were asymptomatic, none extended to the IVC, none were treated with anticoagulants and none of the patients developed symptoms of PE on follow-up (Yassa & Ryst, 1999).

Recommendation

1 Post-partum ovarian vein thrombosis should be treated with conventional anticoagulation for 3–6 months as for other cases of post-partum VTE (1C).
2 Incidentally identified ovarian vein thrombosis in patients who have undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy with retroperitoneal lymph node dissection does not require anticoagulation except in the rare patient with IVC extension or PE (2C).

Penile vein thrombosis

Venous thrombosis of the penis, or Mondor disease, is superficial vein thrombosis of the dorsal penile vein. It is a benign condition presenting with pain and a palpable cord like thrombosis on the dorsal aspect of the penis, occasionally extending to the suprapubic area. Although trauma, hypercoagulability and thrombophilia have been proposed as predisposing factors there are no good studies to confirm causality. The diagnosis can be confirmed by ultrasound scanning but is not always required. Treatment is geared towards pain relief. Haematological investigation is not indicated and anticoagulation is not required because embolism does not occur and spontaneous resolution occurs within 6–8 weeks (Griger *et al*, 2001).

Recommendation

1 Dorsal penile vein thrombosis is a benign condition that requires neither thrombophilia investigation nor anticoagulant treatment (2C).

Superficial vein thrombosis of the lower limb

Superficial venous thrombosis (SVT) of the lower limb, involving long or short saphenous veins or their branches, is possibly even more common than DVT of the leg (Blumenberg *et al*, 1998; Di Minno *et al*, 2005). Two thirds of cases are seen in females and three quarters occur in an existing varicose vein (Decousus *et al*, 2010a). Risk factors for SVT are essentially the same as for DVT (Di Minno *et al*, 2005; Di Nisio *et al*, 2007) and SVT itself contributes 5·4% (95% CI 3·0–7·7) of the adjusted population attributable risk for first DVT or PE event (Heit *et al*, 2002). Pregnancy is associated with an increased risk of SVT, similar to that of DVT, most commonly post-partum (McColl *et al*, 1998; Olson & Nunnelee, 1998). Heritable thrombophilia is an aetiological factor; indeed, SVT has been reported as the first manifestation of venous thrombosis in 11–15% of patients with protein C or S deficiency and around 40% of those with *F5* R506Q (Engesser *et al*, 1987; de Moerloose *et al*, 1998; Martinelli *et al*, 1998b; Allaart *et al*, 1993). However there are no data to suggest that the presence of a thrombophilia should alter management or influence rates of SVT recurrence or progression.

Studies on the epidemiology and natural history of SVT have focused on cases referred to hospital or vascular laboratories for assessment, and therefore are likely biased towards the more clinically severe forms of the condition. Nevertheless, it is evident that what historically was regarded as a benign self-limiting condition can progress to DVT and

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cause PE. In a prospective study of 844 consecutive cases of SVT measuring at least 5 cm in length, Decousus *et al* (2010a) demonstrated that 24·9% had concurrent VTE at diagnosis (3·9% with symptomatic PE, 9·7% proximal DVT and 11·3% distal DVT). In only 58% of cases was the DVT contiguous with the SVT. Concomitant DVT is less likely with SVT at the site of an existing varicose vein, but more likely if the SVT involves the main trunk of a saphenous vein (rather than its branches), particularly the proximal long saphenous vein if adjacent to the sapheno-femoral junction or within 10 cm of it (Ascer *et al*, 1995; Hanson *et al*, 1998; Decousus *et al*, 2010a).

Isolated SVT (without concomitant DVT) may still progress to DVT. In an ultrasound follow-up study of 263 cases of untreated isolated SVT, 11% had progressed to DVT within 10 d (Chengelis *et al*, 1996). Even with LMWH therapy (approximately 63% full dose and 37% prophylactic dose; median duration 11 d) in 586 cases of isolated SVT, Decousus *et al* (2010a) documented 10·2% with further venous thrombosis (0·5% symptomatic PE, 2·8% symptomatic DVT, 3·3% SVT extension and 1·9% recurrent SVT) during 3 months follow-up. Risk factors for SVT extension, recurrence or progression to DVT include: SVT within 10 cm of the sapheno-femoral junction, male sex, history of VTE, cancer, absence of varicose veins and severe chronic venous insufficiency (Quenet *et al*, 2003; Decousus *et al*, 2010a,b). SVT adjacent to (within 3 cm of) the sapheno-femoral junction has such a high risk of progression to DVT (14–70%) that such patients are no longer included in interventional trials in SVT, but rather given therapeutic anticoagulation as for DVT (Ascer *et al*, 1995; Chengelis *et al*, 1996; Prandoni *et al*, 2005; Decousus *et al*, 2010a,b).

Although often diagnosed clinically, there is now a strong argument for ultrasound assessment of SVT to identify those cases with concomitant DVT or SVT at the sapheno-femoral junction, both of which merit therapeutic anticoagulation – the latter formerly being subject to surgical intervention until anticoagulation was shown to be as effective and possibly safer (Ascer *et al*, 1995; Di Nisio *et al*, 2007). D-dimer has an inadequate sensitivity and negative predictive value for SVT (Binder *et al*, 2009) and has not been properly assessed for sensitivity and specificity for concomitant DVT in the presence of SVT.

A Cochrane review (Di Nisio *et al*, 2007) of therapeutic trials in SVT found that topical preparations [non-steroidal anti-inflammatory drugs (NSAIDs), heparins and heparinoids] did provide symptom relief but there was no evidence of their efficacy in preventing SVT extension, recurrence or progression. The Superficial Thrombophlebitis Treated By Enoxaparin Study Group (2003) reported that, compared to placebo, 8–12 d of subcutaneous prophylactic or therapeutic LMWH or oral NSAIDs were all safe and significantly reduced the risk of SVT extension or recurrence by approximately 67%, a benefit which was maintained through 3 months follow-up. Although underpowered to show superiority in preventing progression to VTE, there was a trend to lower VTE rates in the LMWH arms at the end of the treatment period (but not at 3 months follow-up). One month of prophylactic dose LMWH was as effective as therapeutic doses in terms of symptom resolution and rates of SVT extension, recurrence and progression during 3 months follow-up (Prandoni *et al*, 2005). To date, the largest placebo-controlled double-blind randomized trial in 3000 cases of isolated SVT assessed the safety and efficacy of prophylactic dose fondaparinux (2·5 mg daily) for 45 d (Decousus *et al*, 2010b). SVT at or within 3 cm of the sapheno-femoral junction were not included in this study. There was no excess bleeding and relative risk reduction for symptomatic DVT or PE at final follow-up (77 d) was 82% (95% CI, 47–94%) in the treatment arm (absolute rate 0·3% vs. 1·5%).

Recommendation

1 Patients with lower limb SVT should have ultrasound assessment to exclude DVT, particularly if affecting the proximal long saphenous vein (1B).
2 Patients with confirmed SVT within 3 cm of the sapheno-femoral junction should be considered for therapeutic anticoagulation (2B).
3 Patients with SVT and risk factors for extension, recurrence or progression should be offered treatment with prophylactic doses of LMWH for 30 d (currently an unlicensed indication) or fondaparinux for 30–45 d (1B).
4 Other patients with SVT should be offered 8–12 d NSAIDs unless contraindicated (1A).
5 Investigation of patients with SVT for underlying thrombophilia is not routinely indicated, and should follow existing guideline criteria (1B).

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While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

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