Guideline on the investigation, management and prevention of venous thrombosis in children.
British Committee for Standards in Haematology

Address for correspondence:
BCSH Secretary
British Society for Haematology,
100 White Lion Street,
London.
N1 9PF.
e-mail bcsh@b-s-h.org

Writing group:
EA Chalmers¹, VJ Ganesen², R Liesner², S Maroo¹, TJC Nokes³, D Saunders², MD Williams⁴.

Disclaimer:
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.

Date for Guideline Review:
December 2015

¹Royal Hospital for Sick Children, Glasgow, UK
²Great Ormond Street Hospital, London UK
³Derriford Hospital, Plymouth
⁴Birmingham Children’s Hospital, Birmingham, UK
Table of contents:

Summary .............................................................................................................................................3

Introduction .........................................................................................................................................3

Methodology ........................................................................................................................................4

1 Diagnositc imaging ..........................................................................................................................5

2 Laboratory investigation ..................................................................................................................9

3 Management ...................................................................................................................................Error! Bookmark not defined.

4 Prophylaxis ......................................................................................................................................Error! Bookmark not defined.

5 Therapeutic agents and dosing recommendations ..........................................................................5

Conflict of interest declaration .........................................................................................................Error! Bookmark not defined.8

Grading of evidence and recommendations ......................................................................................Error! Bookmark not defined.9

References ............................................................................................................................................30
Summary
Venous thrombo-embolism (VTE) is increasingly recognised in paediatric practice. Few clinical trials have been performed in this area in children and management is largely extrapolated from adult practice where there is a considerable evidence base. This is likely to be unsatisfactory for a number of reasons. Firstly, there are significant differences in epidemiology and potential differences in the mechanisms for VTE in this age group. Secondly, many aspects of haemostasis are age-dependant which has implications for the use of anticoagulants in the paediatric population. Thirdly, there are very limited data available on the safety and efficacy of anticoagulants to manage specific indications in paediatric practice, often with limited paediatric formulations available. In addition, children may survive for a prolonged period following these events so that long term consequences may be highly significant in this age group. The aim of this guideline is to provide a rational basis for the investigation and management of children age 1 month–16 years with VTE, including cerebral venous thrombosis (CVT). The guideline is targeted at healthcare professionals involved in the management of children and adolescents with VTE, particularly paediatric haematologists.

Introduction
The annual incidence of VTE in children has been estimated at 0.7 to 1.0 per 100,000 population with a prevalence of 5.3 per 10,000 hospital admissions according to the Canadian VTE registry (Andrew M et al. 1994) and these figures are in good agreement with more recent national registries (Van Ommen et al., 2001; Gibson et al, 2004; Newall F et al, 2006a). There is a bimodal distribution with peaks in the neonatal period and in adolescence. Cerebral (sinus) vein thrombosis (CVT) is also increasingly diagnosed owing to improved recognition of clinical symptoms and the availability of cerebrovascular imaging (Chan et al. 2003).
Several features distinguish childhood VTE from VTE in adults, particularly the high frequency of secondary events (Chalmers, 2006). In children over 90% of events are related to underlying medical or surgical risk factors (van Ommen CH et al, 2003) of which central venous lines (CVL) are the most important (Revel-Vilk S et al, 2003). In keeping with this there is a high incidence of upper extremity thrombosis in children. A number of adverse clinical outcomes are reported following VTE in children (Monagle P et al. 2000). In the Canadian registry, mortality directly attributable to VTE occurred in 2.2%, with recurrent thrombosis in 8.1% and post-thrombotic syndrome (PTS) in 12.4% with an average follow-up period of 2.86 years (Monagle P et al. 2000).

**Methodology**

This guidance was produced with reference to relevant publications since 1990. Publications known to the writing group were supplemented with additional papers identified by searching PubMed for publications in the last 20 years using key words (venous thrombosis, cerebral vein thrombosis, sino-venous thrombosis) and limits (humans, children, core clinical journals, English language).

The writing group produced a draft guideline which was subsequently reviewed by the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology (BCSH) and the sounding board of the British Society of Haematology, comments being incorporated where appropriate.

Criteria used to define strength of recommendations and levels and grades of evidence are according to the GRADE system (Guyatt et al 2006). Strong recommendations (grade 1, ‘recommended’) are made when there is confidence that the benefits either do or do not outweigh the harm and costs of treatment. Where the magnitude of benefit or not is less certain, a weaker grade 2 recommendation (‘suggested’) is made. Grade 1 recommendations can be applied uniformly to most patients whereas grade 2 recommendations require a more individualized application. The quality of evidence is graded as A (high
quality randomized clinical trials), moderate (B), low (C). More information on the grading of evidence can be found at the end of the document.

1. Diagnostic imaging

1.1 Diagnosis of CVL and non-CVL related VTE in the upper limb (UL)
There are few studies looking at the assessment of CVL-related VTE of the UL in children. The PARKAA study was a multicentre randomized controlled trial (RCT) evaluating the incidence of VTE in children with acute lymphoblastic leukemia (ALL) and a CVL (Male et al, 2002). Venography was more sensitive than ultrasound (US) in the detection of central (intrathoracic) VTE (83-100% vs. 0-33%) whereas US was more sensitive than venography in the detection of thrombosis of the internal jugular and axillary veins (50%-75% vs. 25% to 50%). The overall sensitivity of US for the detection of CVL-related VTE in the central veins was only 37%. Venography was unable to detect VTE in the jugular veins resulting in an overall sensitivity of 79%. The authors concluded that US alone could result in the failure to detect significant intra-thoracic VTE and therefore recommended that both modalities are when investigating the upper venous system for VTE in children.

In adult patients three-dimensional gadolinium-enhanced magnetic resonance venography (MRV) has been shown to be 100% sensitive and specific for the diagnosis of abnormalities affecting large central veins. There are limited data on the use of MRV in children with suspected CVL-related VTE and no studies have compared MRV to other forms of imaging in this age group (Miga et al, 1997; Shankar et al, 2002; Chalmers et al, 2003;). MRV is, however, non invasive and may be preferable, especially where contrast venography is contraindicated.

Recommendations
1. US is recommended for the initial assessment of the peripheral upper limb, axillary, subclavian and internal jugular veins but may be relatively insensitive for the detection of central intra-thoracic VTE. (1B)
2. Contrast MRV is recommended for assessing the central veins for VTE. (1C)

3. Multi-detector CT venography (MDCT venography) may be considered for the assessment of the central veins if MRV is unavailable. MRI should always be preferred to CT due to radiation dose considerations in children. (2C)

1.2 Diagnosis of CVL and Non-CVL related VTE in the lower extremity (LL)
There is little data on the use of US in non-catheter related VTE of the LL in children and recommendations are extrapolated from adult studies. In adults US has been shown to have high sensitivity and specificity for the diagnosis of proximal vein VTE of the LL (Kearns C et al, 1998). Similar results have been obtained with MRV for the diagnosis of femoral and iliac vein VTE (Fraser et al, 2003).

Recommendations:
1. Doppler US is recommended to assess the LL venous system for VTE. (1B)
2. If the US is normal and the clinical suspicion of VTE remains high this should be repeated after a week to assess for proximal progression of any calf vein thrombus. (1C)
3. MRV should be considered in children with suspected proximal extension of femoral VTE. (2C)

1.3 Investigation of a blocked CVL
Investigation of a potentially occluded CVL is necessary if the line fails to function, particularly if this persists following the local instillation of a thrombolytic agent. A frequent problem is the formation of a fibrin sheath or thrombosis in the CVL or associated vessels.
Flow problems, particularly soon after placement, may be secondary to a catheter kink, a malpositioned tip or a constricting suture. These can be
demonstrated by a conventional chest radiography or contrast linogram (Santilli et al, 2002). Unless the catheter is completely occluded the presence of a fibrin sheath is best diagnosed by a contrast linogram, which can be diagnostic for both low and high flow catheters. Contrast linograms cannot however exclude the presence of asymptomatic large vessel thrombosis which will require alternative imaging techniques (See section 1.1).

Recommendations:
1. A chest X-Ray is recommended to visualize the CVL position. (2C)
2. A contrast linogram is recommended to determine potential occlusion at the tip of the CVL and presence of retrograde flow. (2C)
3. Surveillance for asymptomatic VTE is not recommended. (2C)
4. Doppler US, conventional venography or contrast enhanced MRV may be required to exclude large vessel thrombosis. (2C)

1.4 Diagnosis of PE
In children no studies are available assessing the diagnostic utility of imaging tests for PE. Recommendations are therefore based on the feasibility of these techniques in children and evidence from adult studies (BTS, 2003). None of the existing imaging modalities have a 100% diagnostic specificity or sensitivity particularly when it comes to subsegmental vessel emboli (Nilsson et al, 2001).

Recommendations:
1. If available, isotope lung scanning may be considered as the initial imaging investigation providing the chest X-ray is normal and there is no significant concurrent cardiopulmonary disease. Otherwise CT pulmonary angiography (CTPA) is recommended as the initial imaging modality for suspected PE. (1B)
2. Non-diagnostic isotope lung scanning should be followed by further imaging. (1B)
3. Patients with a good quality negative CTPA do not require further investigation or treatment. (1B)

4. Pulmonary magnetic resonance angiography (MRA) should be considered as an alternative to CTPA when iodinated contrast injection or radiation is a significant consideration. (2C)

1.5 Diagnosis of CVT

The diagnosis of CVT relies on either the detection of an intravascular thrombus or an occluded vessel. In as many of 25% of individuals, conventional brain imaging is normal and the classical imaging appearance of multiple haemorrhagic infarcts, not conforming to an arterial territory, is relatively uncommon. Other radiological features of CVT include basal ganglia and thalamic infarcts that are usually not haemorrhagic and are secondary to deep venous sinus thrombosis.

As with other aspects of childhood thrombosis, comparative studies of different imaging techniques have only infrequently been carried out in children. Therefore, recommendations are based on small paediatric studies and extrapolation from adult data. In addition, although the traditional gold standard for the investigation of suspected CVT in children is the venous phase of a conventional cerebral angiogram (CA), this is an invasive procedure, with associated risks and is now infrequently performed in children. Subsequently, this has been replaced by non-invasive MRI and MRV, with associated difficulties in determining the sensitivity and specificity.

A number of studies have been performed comparing CT and MRI/MRV in the investigation of CVT Dormont et al, 1994; Lafitte et al, 1997; Oswarth et al, 1997; de Veber et al, 2001; Idbaih et al, 2006. The available data suggest that MRI/MRV is even more sensitive than CT for the detection of CVT, which is in itself very sensitive. The imaging recommendations 1-4 are made as a result of these comparative studies, and are pragmatic in that MRI is not always available in emergencies but rapid diagnosis of CVT is essential. Both CT and MRI are sensitive to the early detection of haemorrhagic infarcts, seen in a significant
proportion of patients. In de Veber’s cohort, 37 non-neonates had infarcts of which 21 were haemorrhagic (de Veber et al, 2001).

Although CT venography (CTV) has been shown to be as sensitive as MRI/MRV for the detection of normal sinuses, there is no published data on its role in the evaluation of children with CVT. As CTV is more invasive, involving both the need for contrast administration and ionising radiation, MRI and MRV are recommended in preference to CTV, however, CTV may be of value in children who do not have access to MRV.

Recommendations:
1. Children in whom CVT is suspected should have urgent brain MRI including T2* imaging and MRV to detect both intraparenchymal haemorrhage and sinus thrombosis. (1B)
2. If urgent MRI is unavailable, a pre- and post-contrast CT scan with CT venography (CTV) should be performed as a first line investigation to detect both intraparenchymal haemorrhage and sinus thrombosis (1B).
3. Imaging should include the petrous temporal bones and air filled sinuses to establish sinusitis/mastoiditis as a potential cause for CVT (1C).
4. Children in whom CVT is suspected on CT could have confirmatory MRI replaced by CTV if MRI/MRV is not available (1C).
5. Conventional cerebral angiography could be considered for those children with suspected cortical vein thrombosis not confirmed on MRI/MRV. (2B).

2. Laboratory Investigation of VTE

2.1 Acute VTE
VTE can occur as a complication of various systemic disorders which should be excluded by appropriate investigations. Laboratory investigations should also
establish the safety of initiating anticoagulation and should include a full blood count and baseline coagulation screen. Whereas the negative predictive value of measurement of D-Dimer for VTE diagnosis has been validated in adults its use in children has not been validated (Stein et al, 2004). D-Dimer levels may vary with age in children and results may therefore be difficult to interpret (Sosothikul, 2007).

**Recommendations:**
1. Laboratory investigations are required to aid the exclusion of systemic disorders in children presenting with a suspected VTE. (1C)
2. Haematology investigations (FBC, clotting screen) and renal function should be undertaken to confirm safe baselines prior to anticoagulation. (1C)
3. D-Dimers should not be used to exclude VTE in children. (2C)

**2.2 Heritable and acquired thrombophilia**

**2.2.1 Acute VTE** The reported prevalence of thrombophilic defects in children with VTE varies between 10-78 % (Andrew et al, 1994; Bonduel et al, 2000; Ehrenforth et al, 1999; Hagstrom et al, 1998; Nowak-Göttl et al, 2001; Revel-Vilk et al, 2003; Schobess et al, 1999; van Ommen et al, 2001; van Ommen et al, 2003). This likely reflects differences in patient populations, definitions of thrombosis, investigations undertaken and study size. Deficiencies of antithrombin, protein C or protein S, the presence of the Factor V Leiden and the prothrombin 20210A gene mutations have been reported in these cohorts, as have hyperhomocysteinaemia, increased lipoprotein (a) levels and elevated plasma levels of factor VIII. The contribution of such abnormalities to the aetiology of childhood thrombosis remains uncertain, though they are widely believed to be contributory.

Given the lack of conclusive data, the issue of screening for heritable thrombophilia in childhood VTE remains controversial. At present, the finding of such defects does not routinely influence the initial management of a child with a
VTE. The presence of specific or combined thrombophilic defects may be associated with a higher risk of recurrent thrombosis (Nowak-Göttl et al, 2001; Young et al, 2009). However, there are not enough data to determine whether the presence of a thrombophilic defect should influence the duration of anticoagulation (Raffini and Thornburg, 2009). In adults studies, the clinical utility of testing asymptomatic relatives of symptomatic thrombophilia carriers has not been demonstrated (Baglin, 2010). Targeted testing of relatives of individuals with “higher-risk” defects has been proposed (De Stefano 2004, Spencer and Goldberg 2005). Similarly, in paediatric practice testing asymptomatic children with a positive family history of a thrombophilic defect is controversial and at present there is no clinical evidence base to support this practice. Given the uncertain clinical utility careful consideration should be given to the potential medical benefit of testing children for heritable thrombophilic defects. Ideally testing for genetic abnormalities should be delayed until children are of an age to understand the implications of test results and this is usually best deferred until they are adults and can give informed consent before the tests are performed.

The persistence of elevated levels of D-Dimer has been shown in adults to be related to recurrence of thrombosis (Palareti et al, 2002; Eichinger, 2003; Palareti, 2006) and has been proposed as an indication for prolongation of anticoagulation, though such a proposal remains controversial (Baglin, 2006; Verhovsek et al 2008). Similarly, elevated factor VIII levels may be associated with an increased risk of recurrent thrombosis (Legani, 2004), as may other inflammatory markers. Such markers may also be significant in children but the data is limited in this population: to date, one paediatric study has reported the presence of elevated factor VIII and D-dimer levels to predict poor outcome of thrombosis (Goldenberg, 2004). At present these markers cannot be recommended in isolation in determining the duration of anticoagulation in children.

Children with unprovoked VTE and persistent lupus anticoagulant or anti-β2-glycoprotein-1 antibodies appear to be at increased risk of recurrent thrombosis.
and should be considered for long term anticoagulation (Nuss et al, 1997; Goldenberg et al, 2004) with treatment reviewed throughout childhood.

Recommendations:
1. Routine testing for heritable thrombophilia in unselected children presenting with a first episode of VTE is not indicated (1B).
2. Initiation and intensity of anticoagulant therapy following a diagnosis of acute VTE should be the same in children with and without heritable thrombophilia (1B).
3. Testing for heritable thrombophilia after a first episode of VTE has uncertain predictive value for recurrence. Decisions regarding duration of anticoagulant therapy in relation to the results of testing for heritable thrombophilia, factor VIII levels and D-dimer are not evidence based and are not recommended as sole determining factors for the duration of anticoagulation in children (1B).
4. Children presenting with an unprovoked VTE should be tested for the presence of anti-phospholipid antibodies and those with persistently positive results should remain on long-term anticoagulation (1B).

2.2.2 Purpura fulminans & early onset spontaneous thrombosis. Purpura fulminans (PF) is a rare syndrome characterised by progressive haemorrhagic skin necrosis that occurs in neonates with congenital severe protein C deficiency at birth or in the first few days of life, and in association with infection in children and adults. PF is also observed inherited and acquired protein S deficiency. Neonates and children with purpura fulminans should be tested urgently for protein C and S deficiency with results interpreted using age adjusted normal ranges.

Homozygous type I antithrombin (AT) deficiency is probably incompatible with life. Less severe defects may however present early in life with unexplained venous and arterial thrombotic events. Children with early onset spontaneous
thrombotic events should be screened for AT deficiency as this may alter acute management

Recommendations:

1. Neonates and children with purpura fulminans should be tested urgently for protein C and S deficiency (1B).
2. Children with early onset spontaneous thrombotic events should be screened for AT deficiency (1C).

3. Management of VTE

The aims of antithrombotic therapy in children with VTE are firstly to reduce the risk of death due to thrombus extension or embolisation; secondly, to reduce the incidence of recurrent thrombosis; thirdly, to reduce the incidence of PTS by limiting vascular damage and fourthly, to maintain vessel patency in those with ongoing requirements for vascular access. These aims are therefore broadly similar to those for adults with VTE, as are the anticoagulant agents in current use.

The management of childhood VTE is often complex, which in part reflects the frequent co-existence of other medical and surgical problems in these children. The agents most frequently used are unfractionated heparin (UFH), low molecular weight heparin (LMWH) and the oral vitamin K antagonists (VKA). Many aspects of the haemostatic system are age dependent and this has implications for the use of anticoagulants in this age group. Despite this there is only limited data available on the efficacy and safety of these drugs for the management of specific indications in paediatric practice, which is reflected in the evidence levels contained in current guidelines.

Anticoagulant services are less well developed in paediatric practice but there is an increasingly requirement in tertiary centres for clinicians to develop expertise
in the management of these problems and to establish nurse specialist led outpatient anticoagulant services for this patient group.

3.1 Anticoagulant therapy.
To date there is only one published RCT addressing the efficacy and safety of different anticoagulant regimens in children with VTE. In the REVIVE study 78 children with a first episode of VTE were randomised to receive either LMWH (reviparin-sodium) (N=37) or UFH followed by oral anticoagulation (UFH/VKA) (N=41) (Massicotte et al, 2003a). This study was underpowered due to early closure but showed LMWH to be effective with a low risk of bleeding and there was no suggestion that LWMH resulted in inferior outcomes compared with UFH/OA.

Four observational studies have addressed the use of LMWH in the management of children with VTE and have reported various data on safety and efficacy. The largest of these studies by Dix et al reported results from 146 courses of LMWH administered for the treatment of VTE in both neonates and older children (Dix et al, 2000). A clinical response to treatment was reported in 94% of cases, recurrent VTE occurred in 1% and major bleeding in 5% (Dix et al, 2000). Punzalon et al in a smaller study of 14 patients, again including both neonates and children reported clinical improvement in 100%, with no documented major bleeding (Punzalon et al, 2000). Two other small studies also appear to confirm a low risk of major bleeding (Massiccotte et al, 1996; Nohe et al, 1999).

Comparing these data with older observational studies using UFH/VKA is limited as most of these studies report on the use of these agents in a variety of different clinical situations and do not specifically deal with VTE (Andrew et al, 1994; Streif et al, 1999). While comparative data on efficacy is limited, some information is available on the overall risk of bleeding. Andrew et al in a prospective cohort study recorded mild bleeding in 1.9% of 65 children receiving UFH, including 30
with DVT/PE and the incidence of major bleeding in children receiving long term oral anticoagulation has been reported in a large cohort study as 0.5% per patient year (Andrew et al, 1994; Streif et al, 1999).

Data on clinical management has also come from several large national registries which have been reported from Canada, the Netherlands and most recently from the UK (Andrew et al, 1994; van Ommen et al, 2001; Gibson et al, 2004). These registries have demonstrated a clear trend towards the increasing use of LMWH over the last decade with a corresponding reduction in the use of UFH and VKA.

In adults initial therapy with either UFH or LMWH followed by VKA therapy is recommended as the treatment of choice for most patients (Baglin et al, 2005). In children the choice of agent depends on a number of factors including age, co-existing conditions and compliance. Although either UFH or LMWH may be used for initial therapy, LMWH is the more frequently used agent in clinical practice. UFH has disadvantages in terms of venous access, frequent monitoring and poor bioavailability; however, in particularly in post operative or critical care settings the short half-life and easy reversibility may have advantages. For ongoing management, while VKA therapy may be appropriate for some children, for others, particularly those with complex co-existing problems, the use of LMWH may have significant practical advantages. VKA control is particularly problematic in very young children and may also be difficult in those receiving multiple concomitant medications or in those with frequent requirements for surgical and other interventions and a where there is a high risk of bleeding.

3.1.1 Treatment intensity. Only limited data are available on the optimal intensity of warfarin therapy in the management of childhood VTE. It has been shown that children receiving warfarin have decreased and delayed thrombin generation when compared with adults and also have reduced concentrations of prothrombin fragment 1+2, suggesting that they may require less intense
treatment (Massicotte et al, 1998). These data are supported by in vitro studies in animals but have yet to be validated in clinical studies in children and in the absence of this information the target INR continues to be based on adult data. A target INR of 2.5 is therefore generally accepted as being appropriate for the management of childhood VTE.

Recommendation:
1. Anticoagulation should be initiated with LWMH followed by warfarin (INR 2.5) or continuing LMWH. (1B) UFH may be used for initial therapy where rapid reversal of anticoagulation may be required. (2C) Ongoing therapy with LMWH may be preferable in infants under 1 year of age. (2C)

3.1.2 Treatment duration. There are no published studies addressing the risk-benefit ratio of different treatment durations in the management of childhood VTE. Children with idiopathic DVT are usually treated for 6 months while those with a secondary DVT, where the risk factor has resolved or been removed, may be treated for a shorter period of time, usually up to 3 months. CVL-related thrombosis represents a very significant proportion of childhood VTE. It has been suggested that children with uncomplicated CVL-related VTE, who have rapid resolution of their thrombosis following initial anticoagulant therapy and CVL removal could be managed with a shorter course of anticoagulation (Manco-Jonhson, 2006). This is unproven at the present time but is the subject of ongoing studies which if successful may facilitate shorter duration therapy in this group of children. Children with recurrent idiopathic DVT appear to be at high risk of further recurrence and should receive lifelong anticoagulation (See also Laboratory Investigation section).

Recommendations:
1. Duration of anticoagulation should be up to 3 months in secondary VTE and 6 months in idiopathic VTE. (1C)
2. Recurrent idiopathic VTE and children with antiphospholipid syndrome: duration life-long. (1C)

3.2 Thrombolytic therapy
Thrombolytic therapy offers the possibility of achieving more rapid relief of vessel occlusion than is likely to be achieved with conventional anticoagulant therapy but is associated with an increased risk of bleeding. Both urokinase (UK) and tissue plasminogen activator (t-PA) have been used successfully in children, however, indications for treatment and optimal dosing regimens have not been established.

T-PA is the agent of choice in children based on its low immunogenicity and in vitro clot lysis data which is superior than that achieved with either streptokinase or UK (Gupta et al, 2001). The most commonly used regimen is t-PA 0.1-0.6 mg/kg/hr with re-evaluation after 6 hours. Although variable outcomes have been reported recent data have suggested a reduced risk of PTS in children with high risk lower limb DVT (Goldenberg, 2007). In addition, successful results have been reported in a small cohort study using a low dose systemic t-PA (0.015-0.06 mg/kg/hr administered for 12-96 hours), which has the advantage of reducing the risk of bleeding (Wang et al, 2003).

In adult practice thrombolysis is not recommended in the routine management of peripheral DVT, although may be considered in cases of major ilio-femoral thrombosis (Buller et al, 2004). Children, particularly those with CVL-related VTE, are at risk for major central venous occlusion involving the pelvic veins, superior vena cava, and inferior vena cava (IVC) and may also develop intra-cardiac involvement. In these circumstances thrombolytic therapy may have advantages over conventional anticoagulation in the early stages of treatment but the risks and benefits of treatment require individual consideration.

Similarly, thrombolytic therapy is not considered appropriate for the routine management of adults with PE, but is recommended in selected cases of
massive PE, particularly those with circulatory collapse or who are haemodynamically unstable (Buller et al, 2008; BTS Guideline, 2003)
Massive PE is uncommon in children but thrombolytic therapy may be appropriate in selected cases with haemodynamic compromise although may be associated with a significant risk of bleeding as was recently observed in a small study where 4/8 children treated with thrombolysis developed major non-fatal haemorrhage (Biss, 2008).

Recommendations:
1. The use of thrombolytic therapy is not indicated for the majority of children with VTE but should be considered in the presence of extensive thrombosis, particularly those involving the pelvic veins, SVC, IVC or intra-cardiac sites. (1C)
2. Thrombolytic therapy should be considered for selected children with massive PE. (1C)

3.3 CVL removal in CVL-related VTE
There are no data on the optimal management of a CVL in the presence of acute CVL-related VTE in childhood and the suggested management is therefore based on expert opinion. As the presence of an indwelling CVL is the single most important risk factor for the development of thrombosis, it is generally recommended that if clinically feasible, the CVL should be removed after an initial 2-4 days of anticoagulation therapy. If the CVL cannot be removed due to problems with venous access then it is important that radiological monitoring is undertaken to look for evidence of thrombus extension.

Recommendation:
- If clinically feasible a CVL associated with either occlusive or non-occlusive VTE should be removed following 2-4 days of therapeutic anticoagulation. (2C)
3.4 IVC filters

The most important indication for the use of IVC filters in both adults and children is the prevention of PE in patients with lower limb VTE in whom systemic anticoagulation is contraindicated either on a temporary or long term basis (Baglin et al, 2006).

In children clinical data on IVC filters are limited to case reports and small case series (Williams, 2003; Cahn et al, 2001; Reed et al, 1996). In one relatively large series, which reported on the placement of 24 filters in 20 children, there were no reported cases of PE documented following placement, although 2 patients did develop thrombosis around the filter (Williams et al, 2003). 23/24 filters were removed after a mean duration of 15 days. Other complications related to difficulties in placement and removal of the filter in 4 children. There are very few reports on the use of permanent filters and in view of potential long term side effects, including thrombosis and filter migration, children should probably only be considered for insertion of removable filters.

In practice although IVC filters are used in children, size is a significant limitation and they are unlikely to be suitable for those weighing <10kg. Their placement may also be limited by a scarcity of appropriately trained and skilled operators (Haider et al 2005, Cahn et al 2001).

Recommendation:

Insertion of a removable IVC filter should be considered in older children with lower limb VTE in whom systemic anticoagulation is contraindicated. (1C)

3.5 Management of CVT

The use of anticoagulation in CVT has been controversial in the past due to its association with intracranial haemorrhage. More recent evidence has shown that it is safe in adults and children. Although, there is no evidence of its efficacy in children, anticoagulation in adults with CVT has been shown to be associated with a reduction in the risk of death and dependency (Stam et al, 2003).
Data from paediatric studies is limited and no RCTs have been performed (de Veber et al, 2001; Heller et al, 2003; Kenet et al, 2004; Sebire et al, 2005). In a Canadian study 85 children (25 neonates) were treated for 3 months with antithrombotic treatment without any deaths or haemorrhagic complications (de Veber, 2001). Sebire et al reported data on 18 children treated with heparin (6 with haemorrhage on imaging), 2 treated with aspirin and one with intravenous tissue plasminogen activator. Again there were no bleeding complications and there was a non-significant trend in the anticoagulated group for better survival and cognitive outcome.

Two other cohort studies, primarily designed to examine the presence of thrombophilic defects in CVT, also reported on the use of anticoagulant therapy in over 85% of cases again without haemorrhagic complications (Heller et al, 2003; Kenet et al, 2004). Thus the available paediatric data suggest that anticoagulation in CVT is safe but do not provide evidence of its efficacy, which is inferred from the studies in adults.

There is no evidence in adults or children that anticoagulation improves rate or frequency of recanalisation. In a study of 33 adults with CVT treated with IV heparin followed by warfarin for at least 4 months, MR imaging was repeated at 4 months and then at 12 months if thrombosis persisted (Baumgartner et al, 2003). Recanalisation was apparent at 4 months if it was going to occur. Strupp et al reported data from 40 patients re-imaged 4-23 years after SVT of whom only 52% demonstrated complete recanalisation (all had been treated acutely with heparin and 35/40 had been subsequently warfarinised) (Strupp et al, 2002). Those in whom there was no recanalisation had significantly more persistent neurological symptoms. Whilst these data do not address the key question of the relationship between anticoagulation and recanalisation, they do emphasise the importance of looking for persistent symptoms and signs of raised intracranial pressure. The significance of lack of recanalisation in the absence of any clinical sequelae, and implications for treatment are not established.
A recent European multicentre study reported data from 396 children with CVT (Kenet et al, 2007). Symptomatic recurrence of VTE was seen in 6%, and related to recurrent intracranial thrombosis in 60%. 70% of recurrent events occurred within 6 months of the index event. Significant risk factors for recurrent thrombosis were presence of the Prothrombin G20210A mutation, age>2 years and failure to recanalise on imaging. Non-administration of anticoagulation was associated with recurrence. It is difficult to draw conclusions from these data regarding the optimal duration of anticoagulant therapy but they suggest that it would be reasonable to recommend 6 months of treatment and then to reassess at that point, with a view to reimaging and more extended anticoagulant therapy in the presence of symptoms or ongoing risk factors for thrombosis.

Ciccone et al undertook a Cochrane review of the evidence supporting the use of thrombolysis in CVT (in all ages) and concluded that there was no data relating to its efficacy (Ciccone et al, 2004).

**Recommendations:**
1. Children with CVT with no associated intra-cranial haemorrhage should be anticoagulated with LMWH or UFH. (1B)
2. In the presence of haemorrhage resulting in a local mass effect or intraventricular haemorrhage it is reasonable to withhold anticoagulation. The presence of less significant intracranial haemorrhage or parenchymal infarction are not contraindications to anticoagulation. (2C)
3. In the event that anticoagulation is not given, reimaging with MRV or CTV is recommended to look for thrombus extension. (2C)
4. Anticoagulation should be continued with warfarin (target INR 2.5) in children over 1 year of age. (1C) LMWH may be preferable in infants under 1 year of age. (2C)
5. Anticoagulation should be continued for
(a) 3 months if there was a clear and treated precipitating factor e.g. infection. (1C)
(b) 6 months if there is no identified precipitant. (1C)
(c) Anticoagulation may need to be continued for longer in patients where there is an ongoing risk factor (e.g. continuing treatment with asparaginase), in those with recurrent idiopathic CVT and in those with ongoing symptoms or signs attributable to venous hypertension (see below); duration should be considered on an individual basis. (2C)
6. Re-imaging should be undertaken prior to stopping anticoagulation in patients with ongoing symptoms attributable to venous hypertension (e.g. headache, vomiting, papilloedema, visual obscurations, visual field deficit) or with progressive neurological signs. Re-imaging is not required in patients with stable neurological signs, unless consideration is being given to extending anticoagulant therapy, in which case it may be helpful to establish whether or not recanalisation has occurred. (2C)
7. There is no evidence to support the routine use of thrombolysis in paediatric CVT. (1C)

4. VTE Prophylaxis in children

General preventative measures should include maintaining adequate hydration, particularly peri and post-operatively, early mobilisation after surgery and removal of CVLs as soon as they are no longer required. In post-pubertal girls undergoing surgery, consideration should be given to withholding the combined contraceptive pill for 4 weeks prior to planned surgery particularly if there is a strong family history of thrombosis or a known thrombophilic risk factor.

4.1 Physical methods for thromboprophylaxis

The use of physical methods for thromboprophylaxis, such as graduated compression stockings (GCS), intermittent pneumatic compression (IPC) devices and venous foot-pumps (VFPs) increase venous outflow and reduce stasis within the leg veins (Amarigiri et al, 2001) but are only realistically applicable to older or
larger children, usually those over 40kg in weight. The evidence to support the use of these devices in all patient groups is significantly less than that for anticoagulant options and few data are available in children and adolescents where compliance may be a particular issue. Generally studies demonstrate effectiveness of all these physical methods in most clinical situations in preventing DVT (Monagle et al, 2008), particularly when the risk for bleeding is high. They have never been shown to reduce the incidence of death or PE.

**Recommendations:**

1. **The use of physical methods for VTE risk reduction should be considered in older children and adolescents who are at increased risk of VTE.** (1C)
2. **In suitable patients physical methods may be helpful when there is a high risk of bleeding or to complement anticoagulant-based prophylaxis when there is a particularly high risk of VTE.** (2C)

**4.2 Pharmacological thromboprophylaxis (UFH, LMWH, VKA):**
The use of anticoagulant agents to prevent VTE has a large evidence base in the adult population, but is very limited in children. LMWHs have become the anticoagulant of choice in the paediatric population, both for treatment and prevention, although none of the preparations is licensed in this age group. The majority of VTEs in children are associated with significant underlying risk factors which are frequently multiple. Adolescents are at higher risk than younger children with the exception of neonates. Excluding CVLs, the most commonly identified risk factors in this age group are sepsis, immobility, malignancy, surgery, congenital heart disease and trauma. Further studies are required to define the highest risk groups and the potential benefits of prophylaxis but in the absence of such data prophylaxis should be considered on an individual basis, particularly in older children with multiple recognised risk factors (Journeycake et al, 2004).
Aspirin is not recommended for VTE prophylaxis in adults and although there are no trials in children, it would seem sensible to follow the same evidence (Geerts et al, 2008). At this time there is very limited data on the use of thromboprophylaxis in children and in general, the risk/benefit ratio for thromboprophylaxis needs consideration on an individual patient basis.

Recommendations:
1. **Children, particularly adolescents, with multiple risk factors for VTE should be considered for thromboprophylaxis with LMWH. (2C)**
2. **There is no evidence for the use of aspirin for VTE prophylaxis in children. (2C)**

4.3 Prevention of CVL-related VTE
A number of studies have identified CVLs as the most significant risk factor for VTE in children. The PARKAA investigators established an increased risk of VTE in children with CVLs, related to location and insertion technique in those receiving L-Asparaginase for ALL and ideally CVLs should not be placed in children with ALL during induction whilst receiving L-Asparaginase .(Male et al, 2003). In this study CVLs sited in the right internal jugular were associated with a lower risk of VTE and placement in the subclavian vein was safer by a cut-down technique rather than percutaneous approach. There is also evidence that femoral CVLs are associated with a particularly high risk for thrombosis in children. The PROTEKT study reported the incidence for VTE as 21/158 children (13%); 32% of these thromboses were associated with femoral CVLs in this prospective, multi-centre cohort study (Male et al. 2005). This compared with an incidence of 27% for subclavian CVLs, 12% for brachial and 8% for jugular, the latter representing a statistically significant difference.

**Recommendation:**
Where possible, CVLs should not be sited in the femoral or subclavian sites, particularly when there is a high risk of thrombosis. (1B)
The PROTEKT trial randomised 186 children to either routine line care or LMWH (reviparin), with a non-significant difference in incidence of VTE in both arms (12.5% v 14.1%) (Massicotte et al, 2003b). In a more recent randomised study, 72 children receiving treatment for various cancers were enrolled to either receive low dose warfarin (INR 1.3-1.9) or to a control group. Asymptomatic VTE was frequent (42%) but not prevented by this low dose warfarin regimen (Ruud et al, 2006). Similarly, adult studies have failed to reproducibly demonstrate benefits related to anticoagulant thromboprophylaxis in this context.

A small prospective cohort study (Newall F et al, 2003) in 8 patients receiving long-term parenteral nutrition has demonstrated improved line survival using VKA (target INR 1.3–1.8 for no previous thrombosis or 2.0–3.0 when previous thrombosis). This approach extended mean CVL patency duration from 161 days to 352 days but did not address CVL-related VTE.

There is evidence from an RCT in a paediatric intensive care unit, that heparin-bonded CVLs have an improved life-span (Pierce et al, 2000). This trial demonstrated in 209 paediatric patients randomised to heparin bonded or non-heparin bonded CVLs, that the incidence of thrombosis was 0% and 8% respectively, with a significantly lower infection rate (4% and 33%).

**Recommendations:**

1. **Thromboprophylaxis for primary prevention of CVL related thrombosis is not recommended.** (2B)
2. **Consideration may be given to the use of heparin-bonded CVLs, if available, for short-term use.** (2C)
5. Therapeutic agents and dosing recommendations for the treatment of VTE in children

5.1 Unfractionated heparin

Initial doses of UFH

*Loading dose;* 75iu/kg over 10 mins IV

*Starting dose;*

*Infants < 1yr* 28iu/kg/hr

*Children > 1yr* 18-20iu/kg/hr

UFH acts via anithrombin and the efficacy of this agent may be reduced in infants with low circulating antithrombin levels.

5.2 LMWH:

*Dalteparin*

100U/kg *twice per day* or 200U/kg *once per day* subcutaneously

*Enoxaparin*

1mg/kg *twice per day* or 2mg/kg *once per day* subcutaneously

*Tinzaparin*

175U/kg *once per day* subcutaneously

*Infants <8 weeks of age and/or <5kg* require 50% larger doses eg Dalteparin 150U/kg *twice per day* and Enoxaparin 1.5mg/kg *twice per day*, possibly due to a larger volume of distribution and/or reduced antithrombin levels.

*Recommended ‘prophylaxis’ doses are usually half treatment doses.*

Target anti-Xa activity taken 4 hours following subcutaneous injection
Therapeutic 0.5-1.0 U/ml  
Prophylactic 0.1-0.4 U/ml

5.3 Warfarin

Initial loading dose of 0.2 mg/kg **orally** for 2 days.
Subsequent dose adjustments should be based on the INR result.

Reversal of warfarin with Vitamin K:
Vitamin K can be given orally or IV, dosing regimens vary but doses or
30 micrg/kg or 0.3-5mg have been reported to be effective (Bolton-Maggs et al, 2002). Prothrombin complex concentrates should be used in the presence of life-threatening haemorrhages.

5.4 Agents used for management of HIT

**Danaparoid sodium (Orgaran):**
Loading dose of 30 U/kg iv bolus
1.2-2.0 U/kg/hr iv to maintain an anti-Xa level of 0.2-0.8 U/ml.
(Bidlingmaier et al, 2006; Monagle et al 2008)

**Lepirudin** (recombinant hirudin)
Lepirudin: 0.1mg/kg/hr by iv infusion is recommended (as per adult dosing).
**A loading dose is not required** and subsequent alterations in dose may be required to achieve an APTT ratio of 1.5-2.5. The dose should be reduced in renal impairment but as it has a short half life of 60-90mins its use is recommended rather than danaparoid.

5.5 Thrombolytic agents

**t-PA**
Recommended doses vary, the following is the most frequently used dose range: 0.1-0.5 mg/kg/hour for 4-6 hours.
Lower doses of 0.015-0.06 mg/kg/hr for 12-96 hours have also been used with success and potentially may reduce the risk of bleeding (Wang et al 2003). t-PA can be given systemically or locally via a catheter-directed approach which allows a lower dose to be administered. Infants have physiologically low levels of plasminogen which may affect the efficacy of tPA and may be enhanced by administering FFP prior to the infusion (Andrew et al, 1992).
Conflicts of Interest:

All authors have filled in a Declaration of Interest form which has been reviewed by the Chair of the Haemostasis and Thrombosis Task Force and the Chair of BCSH and no author is considered to have a conflict of interest with regard to the recommendations made in this guideline.
Grading of the evidence and strength of recommendations
The GRADE Nomenclature:

STRENGTH OF RECOMMENDATIONS:

**Strong (grade 1):** Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

**Weak (grade 2):** Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

QUALITY OF EVIDENCE
The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

**(A) High**  Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

**(B) Moderate**  Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g. inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

**(C) Low**  Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.
References.


Chalmers EA. Epidemiology of venous thrombosis in neonates and children. Thrombosis Research 2006; 118:3-12.


Santilli J. Fibrin Sheaths and Central Venous Catheter Occlusions: Diagnosis and management. Techniques in Vascular and Interventional radiology. 2002; 5:89-94


