Guideline on the investigation, management and prevention of venous thrombosis in children*

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Summary

Venous thrombo-embolism (VTE) is increasingly recognized 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 aged 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.

Keywords: venous thrombosis, paediatric thrombosis, anticoagulation, paediatric haematology, child.

The annual incidence of venous thrombo-embolism (VTE) in children has been estimated at 0·7–1·0 per 100 000 population with a prevalence of 5·3 per 10 000 hospital admissions according to the Canadian VTE registry (Andrew *et al*, 1994a) and these figures are in good agreement with more recent national registries (van Ommen *et al*, 2001; Gibson *et al*, 2004; Newall *et al*, 2006). 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). Over 90% of paediatric events are related to underlying medical or surgical risk factors (van Ommen *et al*, 2003) of which central venous lines (CVL) are the most important (Revel-Vilk *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 *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 *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 (Atkins *et al* 2004). 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

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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) (Guyatt *et al*, 2008a,b; http://www.bcshguidelines.com).

Diagnostic imaging

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 (Prophylactic Anti thrombin replacement in Kids with ALL treated with asparaginase) study was a multicentre randomized controlled trial (RCT) evaluating the incidence of VTE in children with acute lymphoblastic leukaemia (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. 25–50%). 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 used 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 computerized tomography (CT) venography (MDCT venography) may be considered for the assessment of the central veins if MRV is unavailable. Magnetic resonance imaging (MRI) should always be preferred to CT due to radiation dose considerations in children (2C).**

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 (Kearn *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).**

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, 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 Diagnosis of CVL and non-CVL related VTE in the upper limb (UL)].

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).**

Diagnosis of PE

No studies are available assessing the diagnostic utility of imaging tests for PE in children. Recommendations are therefore based on the feasibility of these techniques in children and evidence from adult studies (British Thoracic Society Standards of care Committee Pulmonary Embolism Guideline Development Group, 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).**

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; Osvarth *et al*, 1997; De Veber *et al*, 2001; Idbiah *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 the cohort reported by De Veber *et al* (2001), 37 non-neonates had infarcts of which 21 were haemorrhagic.

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 ionizing radiation, MRI and MRV are recommended in preference to CTV, however, CTV may be of value for children who do not have access to MRV.

Recommendations

1 **Children in whom CVT is suspected should have an 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).**

Laboratory Investigation of VTE

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 *et al*, 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 (full blood count, 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).

Heritable and acquired thrombophilia

Acute VTE.

The reported prevalence of thrombophilic defects in children with VTE varies between 10% and 78% (Andrew *et al*, 1994a; Hagstrom *et al*, 1998; Ehrenforth *et al*, 1999; Schobess *et al*, 1999; Bonduel *et al*, 2000; Nowak-Gottl *et al*, 2001; van Ommen *et al*, 2001, 2003; Revel-Vilk *et al*, 2003). This probably 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 *F5* R506Q (Factor V Leiden) and the *F2* ^{G20210A} 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-Gottl *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 & Thornburg, 2009).

In adult studies, the clinical utility of testing asymptomatic relatives of symptomatic thrombophilia carriers has not been demonstrated (Baglin *et al*, 2010). Targeted testing of relatives of individuals with 'higher-risk' defects has been proposed (Spencer & Goldberg, 2005, De Stefano *et al*, 2006). 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; Palareti *et al*, 2006; Eichinger *et al*, 2003) 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 *et al*, 2004), as might 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 *et al*, 2004). At present these markers cannot be recommended in isolation for 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).

Purpura fulminans and early onset spontaneous thrombosis.

Purpura fulminans (PF) is a rare syndrome characterized 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 in inherited and acquired protein S deficiency. Neonates and children with PF should be tested urgently for protein C and S deficiency and the 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 PF 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).

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 embolization; 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 partly 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.

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 Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE) study, 78 children with a first episode of VTE were randomized 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 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). In a smaller study of 14 patients, again including both neonates and children, Punzalan *et al* (2000) reported clinical improvement in 100%, with no documented major bleeding. Two other small studies also appear to confirm a low risk of major bleeding (Massicotte *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*, 1994b; Streif *et al*, 1999). While comparative data on efficacy is limited, some information is available on the overall risk of bleeding. A prospective cohort study (Andrew *et al*, 1994b) 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 (Streif *et al*, 1999).

Data on clinical management has also come from reports of several large national registries from Canada, the Netherlands and, most recently, from the UK (Andrew *et al*, 1994a; 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, 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.

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 International Normalized Ratio (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

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).

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-Johnson, 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).**

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/h, with re-evaluation after 6 h. Although variable outcomes have been reported, recent data have suggested a reduced risk of PTS in children with high risk lower limb DVT (Goldenberg *et al*, 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/h administered for 12–96 h), 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 (SVC) 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 (British Thoracic Society Standards of care Committee Pulmonary Embolism Guideline Development Group, 2003; Buller *et al*, 2004).

Massive PE is uncommon in children but thrombolytic therapy may be appropriate in selected cases with haemodynamic compromise although it 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 *et al*, 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 intracardiac sites (1C).**
2 **Thrombolytic therapy should be considered for selected children with massive PE (1C).**

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 d 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 d of therapeutic anticoagulation (2C).

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 (Reed *et al*, 1996; Cahn *et al*, 2001; Williams *et al*, 2003). 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 two patients did develop thrombosis around the filter (Williams *et al*, 2003). 23/24 filters were removed after a mean duration of 15 d. Other complications related to difficulties in placement and removal of the filter in four 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 <10 kg. Their placement may also be limited by a scarcity of appropriately trained and skilled operators (Cahn *et al*, 2001; Haider *et al*, 2005).

Recommendation

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

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 *et al*, 2001). Sebire *et al* (2005) reported data on 18 children treated with heparin (six with haemorrhage on imaging), two 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 recanalization. In a study of 33 adults with CVT treated with i.v. heparin followed by warfarin for at least 4 months, MRI was repeated at 4 months and then at 12 months if thrombosis persisted (Baumgartner *et al*, 2003). Recanalization was apparent at 4 months if it was going to occur. Strupp *et al* (2002) reported data from 40 patients re-imaged 4–23 years after CVT, of whom only 52% demonstrated complete recanalization (all had been treated acutely with heparin and 35/40 had been subsequently warfarinized). Those in whom there was no recanalization had significantly more persistent neurological symptoms. Whilst these data do not address the key question of the relationship between anticoagulation and recanalization, they do emphasize the importance of looking for persistent symptoms and signs of raised intracranial pressure. The significance of lack of recanalization 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 *F2* G20210A mutation, age >2 years and failure to recanalize 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*, (2004) 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.

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
(i) Three months if there was a clear and treated precipitating factor e.g. infection (1C).
(ii) Six months if there is no identified precipitant (1C).
(iii) 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 recanalization has occurred (2C).
7 There is no evidence to support the routine use of thrombolysis in paediatric CVT (1C).

VTE Prophylaxis in children

General preventative measures should include maintaining adequate hydration, particularly peri- and post-operatively, early mobilization 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.

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 & Lees, 2010) but are only realistically applicable to older or larger children, usually those over 40 kg 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.

Recommendation

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).

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 licenced 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 recognized risk factors (Journeycake & Manco- Johnson, 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).

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 Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT) study reported the incidence for VTE for 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

1 **Where possible, CVLs should not be sited in the femoral or subclavian sites, particularly when there is a high risk of thrombosis (1B).**
2 **The PROTEKT trial randomized 186 children to either routine line care or LMWH (reviparin), with a non-significant difference in incidence of VTE in both arms (12·5% vs. 14·1%) (Massicotte *et al*, 2003b). In a more recent randomized 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.**
3 **A small prospective cohort study (Newall *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 to 352 d but did not address CVL-related VTE.**
4 **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 randomized 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).**

Therapeutic agents and dosing recommendations for the treatment of VTE in children

Unfractionated heparin

Initial doses of UFH

Loading dose	75 iu/kg over 10 min i.v.
Starting dose	
Infants	<1 year 28 iu/kg/h
Children	>1 year 18–20 iu/kg/h

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

LMWH

Dalteparin: 100 u/kg twice per day or 200 u/kg once per day s.c.

Enoxaparin: 1 mg/kg twice per day or 2 mg/kg once per day s.c.

Tinzaparin: 175 u/kg once per day s.c.

Infants <8 weeks of age and/or <5 kg require 50% larger doses e.g Dalteparin 150 u/kg twice per day and Enoxaparin 1·5 mg/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 h following subcutaneous injection.

Therapeutic 0·5–1·0 u/ml.

Prophylactic 0·1–0·4 u/ml.

Warfarin

Initial loading dose of 0·2 mg/kg p.o. for 2 d.

Subsequent dose adjustments should be based on the INR result.

Reversal of warfarin with Vitamin K: Vitamin K can be given p.o. or i.v., dosing regimens vary but doses of 30 μg/kg or 0·3–5 mg have been reported to be effective (Bolton-Maggs & Brook, 2002). Prothrombin complex concentrates should be used in the presence of life-threatening haemorrhages.

Agents used for management of HIT

Danaparoid sodium (Orgaran): Loading dose of 30 u/kg i.v. bolus 1·2–2·0 u/kg/h i.v. to maintain an anti-Xa level of 0·2–0·8 u/ml (Bidlingmaier *et al*, 2006; Monagle *et al*, 2008).

Lepirudin (recombinant hirudin): 0·1 mg/kg/h by i.v. infusion is recommended (as per adult dosing). A loading dose is not required and subsequent alterations in dose may be required to achieve an activated partial thromboplastin time ratio of 1·5–2·5. The dose should be reduced in renal impairment but as it has a short half-life of 60–90 min its use is recommended rather than danaparoid.

Thrombolytic agents

t-PA.

Recommended doses vary, the following is the most frequently used dose range: 0·1–0·5 mg/kg/h for 4–6 h.

Lower doses of 0·015–0·06 mg/kg/h for 12–96 h 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 fresh frozen plasma prior to the infusion (Andrew *et al*, 1992).

Disclaimer

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References

Amarigiri, SV & Lees, TA. (2010) Elastic compression stockings for prevention of deep vein thrombosis. *Cochrane Database of Systematic Reviews*, Issue 7. Art. No.: CD001484.

Andrew, M, Booker, L & Leaker, M. (1992) Fibrin clot lysis by thrombolytic agents is impaired in newborns due to a low plasminogen concentration. *Thrombosis and Haemostasis*, **68,** 325–330.

Andrew, M, David, M, Adams, M, Ali, K, Anderson, R, Barnard, D, Bernstein, M, Brisson, L, Cairney, B, DeSai, D, Grant, R, Israels, S, Jardine, L, Luke, B, Massicotte, P & Silva, M. (1994a) Venous thromboembolic complications (VTE) in Children: First analyses of the Canadian Registry of VTE. *Blood*, **83,** 1251–1257.

Andrew, M, Marzinotto, V, Massicotte, P., Blanchette, V., Ginsberg, J., Brill-Edwards, P., Burrows, P., Benson, L., Williams, W. & David, M. (1994b) Heparin therapy in pediatric patients: a prospective cohort study. *Pediatric Research;*, **35,** 78–83.

Atkins, D, Best, D, Briss, P.A., Eccles, M., Falck-Ytter, Y., Flottorp, S., Guyatt, G.H., Harbour, R.T., Haugh, M.C., Henry, D., Hill, S., Jaeschke, R., Leng, G., Liberati, A., Magrini, N., Mason, J., Middleton, P., Mrukowicz, J., O'Connell, D., Oxman, A.D., Phillips, B., Schünemann, H.J., Edejer, T.T., Varonen, H., Vist, G.E., Williams, Jr, J.W. & Zaza, S; GRADE Working Group (2004) Grading quality of evidence and strength of recommendations. *BMJ*, **328,** 1490–1494.

Baglin, T. (2006) Value of D-dimer testing to decide duration of anticoagulation after deep vein thrombosis: not yet. *Journal of Thrombosis and Haemostasis*, **4,** 2530–2532.

Baglin, TP, Keeling, DM & Watson, HG. (2005) Guidelines on oral anticoagulation (warfarin): third edition – 2005 update. *British Journal of Haematology*, **132,** 277–285.

Baglin, TP, Brush, J & Streiff, M; on behalf of the BCSH (2006) Guidelines on use of vena cava filters. *British Journal of Haematology*, **134,** 590–595.

Baglin, T, Gray, E, Greaves, M, Hunt, BJ, Keeling, D, Machin, S, Mackie, I, Makris, M, Nokes, T, Perry, D, Tait, RC, Walker, I & Watson, H. (2010) Clinical guidelines for testing for heritable thrombophilia. *British Journal of Haematology*, **149,** 209–220.

Baumgartner, R. W., Studer, A., Arnold, M. & Georgiadis, D. (2003) Recanalisation of cerebral venous thrombosis. *Journal of Neurology, Neurosurgery, and Psychiatry;*, **74,** 459–461.

Bidlingmaier, C, Magnani, H. N, Girisch, M & Kurnik, K. (2006) Safety and efficacy of danaparoid (Orgaran) use in children. *Acta Haematologica*, **115,** 237–247.

Biss, TT, Brandao, LR, Kahr, WH, Chan, AK & Williams, S. (2008) Clinical features and outcome of pulmonary embolism in children. *British Journal of Haematology*, **142,** 808–818.

Bolton-Maggs, P & Brook, L. (2002) The use of vitamin K for the reversal of over warfarinisation in children. *British Journal of Haematology*, **118,** 924.

Bonduel, M, Hepner, M, Sciuccati, G, Torres, AF, Pieroni, G & Frontroth, JP. (2000) Prothrombotic abnormalities in children with venous thromboembolism. *Journal of Pediatric Hematology/Oncology*, **22,** 66–72.

British Thoracic Society Standards of care Committee Pulmonary Embolism Guideline Development Group (2003) British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax* **58**:470–484.

Buller, HR, Agnelli, G, Hull, RD, Hyers, TM, Prins, MH & Raskob, GE. (2004) Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*, **126**(3 Suppl.), 401S–428S.

Cahn, MD, Rohrer, MJ, Martella, MB & Cutler, BS. (2001) Long term follow up of Greenfield inferior vena cava filter placement in children. *Journal of Vascular Surgery*, **34,** 820–825.

Chalmers, EA. (2006) Epidemiology of venous thrombosis in neonates and children. *Thrombosis Research;*, **118,** 3–12.

Chalmers, EA, Mcintosh, N, Gibson, B & Watt, A. (2003) Catheter related thrombosis in children diagnosed by magnetic resonance venography. Abstracts from X1X international ISTH Congress. *Journal of Thrombosis and Haemostasis*, **1**(Suppl. 1), P0045.

Chan, A K, Deveber, G, Monagle, P, Brooker, LA & Massicotte, PM. (2003) Venous thrombosis in children. *Journal of Thrombosis and Haemostasis*, **1,** 1443–1455.

Ciccone, A., Canhao, P., Falcao, F., Ferro, J. M. & Sterzi, R. (2004) Thrombolysis for cerebral vein and dural sinus thrombosis. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD003693.

De Stefano, V, Simioni, P., Rossi, E., Tormene, D., Za, T., Pagnan, A. & Leone, G. (2006) The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S. *Haematologica*, **91,** 695–698.

De Veber, G., Andrew, M., Adams, C., Bjornson, B., Booth, F., Buckley, DJ., Camfield, CS., David, M., Humphreys, P., Langevin, P., MacDonald, EA., Gillett, J., Meaney, B., Shevell, M., Sinclair, DB. & Yager, J.; Canadian Pediatric Ischemic Stroke Study Group. (2001) Cerebral sinovenous thrombosis in children. *The New England Journal of Medicine*, **345,** 417–423.

Dix, D., Andrew, M., Marzinotto, V., Charpentier, K., Bridge, S., Monagle, P., deVeber, G., Leaker, M., Chan, AK. & Massicotte, MP. (2000) The use of low molecular weight heparin in pediatric patients: a prospective cohort study. *Journal of Pediatrics*, **136,** 439–445.

Dormont, D, Anxionnat, R, Evrard, S, Louaille, C & Marsault, C. (1994) MRI in cerebral venous thrombosis. *Journal of Neuroradiology*, **21,** 81–99.

Ehrenforth, S, Junker, R, Koch, H-G, Kreuz, W, Münchow, N, Scharrer, I & Nowak-Göttl, U. (1999) Multicentre evaluation of combined prothrombotic defects associated with thrombophilia in childhood. *European Journal of Pediatrics*, **158**(Suppl. 3), S97–S104.

Eichinger, S, Minar, E, Bialonczyk, C, Hirschl, M, Quehenberger, P, Schneider, B, Weltermann, A, Wagner, O & Kryle, PA. (2003) D-dimer levels and risk of recurrent venous thromboembolism. *JAMA*, **290,** 1071–1074.

Fraser, DG, Moody, AR, Davidson, IR, Martel, AL & Morgan, PS. (2003) Deep venous thrombosis:

diagnosis by using venous enhanced subtracted peak arterial MR venography versus conventional venography. *Radiology*, **226,** 812–820.

Geerts, WH, Bergqvist, D., Pineo, GF., Heit, JA., Samama, CM., Lassen, MR. & Colwell, CW. (2008) Prevention of Venous Thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*, **126,** 338S–400S.

Gibson, BES, Chalmers, EA, Bolton-Maggs, P, Henderson, DJ & Lynn, R. (2004) Thromboembolism in childhood: a prospective two-year BPSU study in the United Kingdom. *British Journal of Haematology*, **125**(Suppl. 1)**,** 1.

Goldenberg, NA., Knapp-Clevenger, R. & Manco-Johnson, MJ; Mountain States Regional Thrombophilia Group (2004) Elevated plasma factor VIII and D-dimer levels as predictors of poor outcomes of thrombosis in children. *New England Journal of Medicine*, **351,** 1081–1088.

Goldenberg, NA, Durham, JD, Knapp-Clevenger, R & Manco-Johnson, MJ. (2007) A thrombolytic regimen for high-risk deep venous thrombosos may substantially reduce the risk of postthrombotic syndrome in children. *Blood*, **110,** 45–53.

Gupta, AA, Leaker, M, Andrew, M, Massicotte, P., Liu, L., Benson, LN. & McCrindle, BW. (2001) Safety and outcomes of thrombolysis with tissue plasminogen activator for treatment of intravascular thrombosis in children. *Journal of Pediatrics*, **139,** 682–688.

Guyatt, GH, Oxman, AD, Vist, GE, Kunz, R, Falck-Ytter, Y, Alonso-Coello, P & Schünemann, HJ. (2008a) GRADE: An emerging concensus on rating quality of evidence and strength of recommendations. *BMJ*, **336,** 924–926.

Guyatt, GH, Oxman, AD, Kunz, R, Falck-Ytter, Y, Vist, GE, Liberati, A & Schünemann, HJ. (2008b) GRADE: going from evidence to recommendations. *BMJ*, **336,** 1049–1051.

Hagstrom, JN, Walter, J, Bluebond-Langner, R, Amatniek, JC, Manno, CS & High, KA. (1998) Prevalence of the factor V Leiden mutation in childen and neonates with thromboembolic disease. *The Journal of Pediatrics*, **133,** 777–781.

Haider, E. A, Rosen, J. C, Torres, C & Valenti, D. A. (2005) Serial repositioning of a Günther tulip retrievable inferior vena cava filter in a pediatric patient. *Pediatric Radiology*, **35,** 1135–1138.

Heller, C., Heinecke, A., Junker, R., Knöfler, R., Kosch, A., Kurnik, K., Schobess, R., von Eckardstein, A., Sträter, R., Zieger, B. & Nowak-Göttl, U; Childhood Stroke Study Group (2003) Cerebral venous thrombosis in children: a multifactorial origin. *Circulation*, **108,** 1362–1367.

Idbiah, A, Boukoba, M, Crassard, I, Porcher, R, Bousser, MG & Chabriat, H. (2006) MRI of clot in cerebral venous thrombosis: high diagnostic value of susceptibility-weighted imaging. *Stroke*, **37,** 991–995.

Journeycake, JM & Manco- Johnson, MJ. (2004) Thrombosis during infancy and childhood: what we know and what we don't know. *Hematology/oncology Clinics of North America*, **18,** 1315–1338.

Kearn, C, Julian, MM, Newman, TE & Ginsberg, JS. (1998) Non invasive diagnosis of deep venous thrombosis. *Annals of Internal Medicine*, **128,** 663–677.

Kenet, G., Waldman, D., Lubetsky, A., Kornbrut, N., Khalil, A., Koren, A., Wolach, B., Fattal, A., Kapelushnik, J., Tamary, H., Yacobovitch, J., Raveh, E., Revel-Vilk, S., Toren, A. & Brenner, B. (2004) Paediatric cerebral sinus vein thrombosis. A multi-center case-controlled study. *Thrombosis and Haemostasis*, **92,** 713–718.

Kenet, G, Kirkham, F, Niederstadt, T, Heinecke, A, Saunders, D, Stoll, M, Brenner, B, Bidlingmaier, C, Heller, C, Knöfler, R, Schobess, R, Zieger, B, Sébire, G & Nowak-Göttl, U; European Thromboses Study Group (2007) Risk factors for recurrent venous thromboembolism in the European collaborative paediatric database on cerebral venous thrombosis: a multicentre cohort study. *Lancet Neurology*, **6,** 595–603.

Lafitte, F, Boukobza, M, Guichard, JP, Hoeffel, C., Reizine, D., Ille, O., Woimant, F. & Merland, JJ. (1997) MRI and MRA for diagnosis and follow up of cerebral venous thrombosis. *Clinical Radiology*, **52,** 672–697.

Legani, C, Cosmi, B, Cini, M, Frascaro, M, Guazzaloca, G & Palareti, G. (2004) High plasma levels of factor VIII and risk of recurrence of venous thromboembolism. *British Journal of Haematology*, **124,** 504–510.

Male, C, Chait, P, Ginsberg, J, Hanna Andrew, K., Halton, M., Anderson, J., McCusker, R., Wu, P., Abshire, J., Cherrick, T., Mahoney, I. & Mitchell, D. L. (2002) Comparision of venography and ultrasound for the diagnosis of asymptomatic deep venous thrombosis in the upper body in children : results of the PARKAA study. Prophylactic Anti thrombin replacement in Kids with ALL treated with asparaginase. *Thrombosis and Haemostasis.*, **87,** 593–598.

Male, C, Chait, P, Andrew, M, Hanna, K, Julian, J. & Mitchell, L.; PARKAA Investigators (2003) Central Venous line-related thrombosis in children: association with central venous line location and insertion technique. *Blood*, **101,** 4273–4278.

Male, C, Julian, JA, Massicotte, P, Gent, M & Mitchell, L; PROTEKT study group (2005) Significant association with location of central venous line placement and risk of venous thrombosis in children. *Thrombosis and Haemostasis*, **94,** 516–521.

Manco-Johnson, M.J. (2006) How I treat venous thrombosis in children. *Blood*, **107,** 21–29.

Massicotte, P, Adams, M, Marzinotto, V, Brooker, L & Andrew, M. (1996) Low molecular weight heparin in pediatric patients with thrombotic disease: a dose finding study. *The Journal of Pediatrics*, **128,** 313–318.

Massicotte, P., Leaker, M., Marzinotto, V., Adams, M., Freedom, R., Williams, W., Vegh, P., Berry, L., Shah, B. & Andrew, M. (1998) Enhanced thrombin regulation during warfarin therapy in children compared to adults. *Thrombosis and Haemostasis*, **80,** 570–574.

Massicotte, P, Julian, JA, Gent, M, Shields, K., Marzinotto, V., Szechtman, B. & Andrew, M.; REVIVE Study Group (2003a) An open-label randomized controlled trial of low molecular-weight heparin and coumarin for the treatment of venous thromboembolic events in children: the REVIVE trial. *Thrombosis Research*, **109,** 85–92.

Massicotte, P, Julian, JA, Gent, M, Shields, K, Marzinotto, V, Szechtman, B, Chan, AK & Andrew, M.; PROTEKT study group (2003b) An open label randomised control trial of low molecular weight heparin for the prevention of central venous line-related thrombotic complications in children; The PROTEKT trial. *Thrombosis Research*, **109,** 101–108.

Miga, DE, McKellar, LF, Denslow, S, Wiles, HB, Case, CL & Gillette, PC. (1997) Incidence of femoral vein occlusion after catheter ablation in children: evaluation with magnetic resonance angiography. *Pediatric Cardiology*, **18,** 204–207.

Monagle, P, Adams, M, Mahoney, M, Ali, K, Barnard, D, Bernstein, M, Brisson, L, David, M, Desai, S, Scully, MF, Halton, J, Israels, S, Jardine, L, Leaker, M, McCusker, P, Silva, M, Wu, J, Anderson, R, Andrew, M & Massiotte, MP. (2000) Outcome of pediatric thrombophilic disease: a report from the Canadian Thrombophilia Registry. *Pediatric Research*, **4,** 763–766.

Monagle, P, Chan, A, Massicotte, P, Chalmers, E. & Michelson, A.D. (2008) Antithrombotic therapy in children: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*, **133,** 887–968.

Newall, FH, Barnes, CB, Savoia, HF, Campbell, J. & Monagle, P. (2003) Warfarin therapy in children requiring long term total parenteral nutrition (TPN). *Paediatrics*, **112,** e386.

Newall, F, Wallce, T, Crock, C, Campbell, J, Savoia, H, Barnes, C & Monagle, P. (2006) Venous thromboembolic disease: a single centre case-series study. *Journal of Paediatrics and Child Health*, **42,** 803–807.

Nilsson, T, Mare, K & Carlsson, A. (2001) Value of structured clinical and scintigraphic protocols in acute pulmonary embolism. *Journal of the Institute of Medicine*, **250,** 213–218.

Nohe, N., Flemmer, A., Rümler, R., Praun, M. & Auberger, K. (1999) The low molecular weight heparin dalteparin for prophylaxis and therapy of thrombosis in childhood: a report on 48 cases. *European Journal of Pediatrics*, **158,** S134–S139.

Nowak-Gottl, U, Junker, R, Kreuz, W, von Eckardstein, A, Kosch, A, Nohe, N, Schobess, R & Ehrenforth, S.; Childhood Thrombophilia Study Group (2001) Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. *Blood*, **97,** 858–862.

Nuss, R, Hays, T, Chudgar, U & Manco-Johnson, M. (1997) Antiphospholipid antibodies and coagulation regulatory protein abnormalities in children with pulmonary emboli. *Journal of Pediatric Hematology/oncology*, **19,** 202–207.

van Ommen, CH, Heijboer, H, Büller, HR, Hirasing, RA, Heijmans, HAS & Peters, M. (2001) Venous

thromboembolism in childhood: a prospective two-year registry in The Netherlands. *The Journal of Pediatrics*, **139,** 676–681.

van Ommen, CH, Heijboer, H, van den Dool, EJ, Hutten, BA & Peters, M. (2003) Pediatric venous thromboembolic disease in one single center: congenital prothrombotic disorders and the clinical outcome. *Journal of Thrombosis and Haemostasis*, **1,** 2516–2522.

Osvarth, RR, Casey, SO, Lustrin, ES, Alberico, RA, Hassankhani, A & Patel, M. (1997) Cerebral venogrpahy: comparison of CT and MR projection venography. *American Journal of Roentgenology*, **169,** 1699–1707.

Palareti, G, Legnani, C, Cosmi, B, Guazzaloca, G, Pancani, C & Coccheri, S. (2002) Risk of venous thromboembolic recurrence: high negative predictive value of D-dimer performed after oral anticoagulation is stopped. *Thrombosis and Haemostasis*, **87,** 7–12.

Palareti, G, Cosmi, B, Legnani Tosetto, C A, Brusi, C, Iorio, A, Pengo, V, Ghirarduzzi, A, Pattacini, C, Testa, S, Lensing, AWA & Tripodi, A. (2006) D-dimer testing to determine the duration of anticoagulation therapy. *The New England Journal of Medicine*, **355,** 1780–1789.

Pierce, CM, Wade, A & Mok, Q. (2000) Heparin-bonded central venous lines reduce thrombotic and infective complications in critically ill children. *Intensive Care Medicine*, **26,** 967–972.

Punzalan, R.C., Hillery, C.A, Montgomery, R.R., Scott, C.A. & Gill, J.C. (2000) Low-molecular weight heparin in thrombotic disease in children and adolescents. *Journal of Pediatric Hematology/Oncology*, **22,** 137–142.

Raffini, L & Thornburg, C. (2009) Testing children for inherited thrombophilia: more questions than answers. *British Journal of Haematology*, **147,** 277–288.

Reed, RA, Teitelbaum, GP, Stanley, P, Mazer, MJ, Tonkin, IL & Rollins, NK. (1996) The use of inferior vena cava filters in paediatric patients for pulmonary embolus prophylaxis. *Cardiovascular and Interventional Radiology*, **19,** 401–405.

Revel-Vilk, S, Chan, A, Bauman, M & Massicotte, P. (2003) Prothrombotic conditions in an unselected cohort of children with venous thromboembolic disease. *Journal of Thrombosis and Haemostasis*, **1,** 915–921.

Ruud, E, Holstrom, H, De Lange, C, Hogstad, EM & Wesenberg, EF. (2006) Low dose Warfarin for the prevention of central line associated thromboses in children with malignancies – a randomised controlled study. *Acta Paediatrica*, **95,** 1053–1059.

Santilli, J. (2002) Fibrin Sheaths and Central Venous Catheter Occlusions: Diagnosis and management. *Techniques in Vascular and Interventional radiology.*, **5,** 89–94.

Schobess, R, Junker, R, Auberger, K, Münchow, N, Burdach, S & Nowak-Göttl, U. (1999) Factor V G1691A and prothrombin G20210A in childhood spontaneous venous thrombosis – Evidence of an age-dependent thrombotic onset in carriers of factor V G1691A and prothrombin 20210A mutation. *European Journal of Pediatrics*, **158**(Suppl. 3)**,** S105–S108.

Sebire, G., Tabarki, B., Saunders, DE., Leroy, I., Liesner, R., Saint-Martin, C., Husson, B., Williams, AN., Wade, A. & Kirkham, FJ. (2005) Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome. *Brain*, **128,** 477–489.

Shankar, KR, Abernethy, LJ, Das, KSV, Roche, CJ, Pizer, BL, Lloyd, DA & Losty, PD. (2002) Magnetic resonance venography in assessing venous patency after multiple venous catheters. *Journal of Pediatric Surgery*, **37,** 175–179.

Sosothikul, D., Seksarn, P. & Lusher, JM. (2007) Pediatric reference values for molecular markers in hemostasis. *Journal of pediatric hematology/oncology*, **29,** 19–22.

Spencer, F.A. & Goldberg, R.J. (2005) Asymptomatic thrombophilia – a family affair. *Journal of Thrombosis and Haemostasis*, **3,** 457–458.

Stam, J., de Bruijn, S. & deVeber, G. (2003) Anticoagulation for cerebral sinus thrombosis. *Stroke*, **34,** 1054–1055.

Stein, PD, Hull, Rd, Patel, KC, Olson, RE, Ghali, WA, Brant, R, Biel, RK, Bharadia, V & Kalra, NK. (2004) D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism : a systematic review. *Annals of Internal Medicine*, **140,** 589–602.

Streif, W., Andrew, M., Marzinotto, V., Massicotte, P., Chan, A.K., Julian, J.A. & Mitchell, L. (1999) Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood*, **94,** 3007–3014.

Strupp, M., Covi, M., Seelos, K., Dichgans, M. & Brandt, T. (2002) Cerebral venous thrombosis: correlation between recanalization and clinical outcome–a long-term follow-up of 40 patients. *Journal of Neurology*, **249,** 1123–1124.

Verhovsek, M., Douketis, J.D., Yi, Q., Shrivastava, S., Tait, R.C., Baglin, T., Poli, D. & Lim, W. (2008) Systematic review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. *Annals of Internal Medicine*, **149,** 481–490.

Wang, M, Hays, T, Balasa, V, Bagatell, R, Gruppo, R., Grabowski, E.F, Valentino, L.A., Tsao-Wu, G & Manco-Johnson, M.J.; Pediatric Coagulation Consortium (2003) Low-dose tissue plasminogen activator thrombolysis in children. *Journal of pediatric hematology/oncology*, **25,** 379–386.

Williams, S, Chait, P, Temple, M, Connolly, B, Chan, AK, Bauman, M, Ash, M & Massicotte, P. (2003) Vena cava filters in children: a review of a single centre clinical experience over 7 years. *Journal of Thrombosis and Haemostasis*, **1**(Suppl. 1)**,** OC439.

Young, G., Becker, S., During, C., Friedrichs, F., Goldenberg, N., Kenet, G., Manco-Johnson, M., Scheffold., C. & Nowak-Gottl, U. (2009) Influence of the factor II G20210A variant or the factor V G1691A mutation on symptomatic recurrent venous thromboembolism in children: an international multicenter cohort study. *Journal of Thrombosis and Haemostasis*, **7,** 72–79.