.Eur J Vasc Endovasc Surg **31**, 667–678 (2006)
doi:10.1016/j.ejvs.2005.11.028, available online at http://www.sciencedirect.com on SCIENCE DIRECT®

Iliofemoral Deep Vein Thrombosis in Childhood; Developing a Management Protocol

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Objective. *To develop an evidence-based protocol for the management of iliofemoral deep vein thrombosis (IDVT) in childhood.*
Methods. *A search of the literature was undertaken. All publications pertaining to IDVT in childhood were analysed and then categorised according to their level of evidence. Recommendations were then made on the basis of this.*
Results. *The commonest presenting symptoms were pain and swelling in the affected limb (evidence level II). Predisposing risk factors of special significance in children included the recent use of a venous access device, malignancy, prothrombotic disorders, infection, surgery and congenital venous anomalies (evidence level II). The most frequently described imaging modalities were B-mode ultrasonography, duplex, venography, and helical CT (evidence level III). The mainstay of treatment was anticoagulation with LMWH alone or followed by warfarin (evidence level I). Early clot removal through catheter-directed thrombolysis or surgical thrombectomy has been shown to be beneficial (evidence level II/III). There is little evidence for the benefit of early mobilisation and compression therapy in childhood.*
Conclusion. *Level I evidence relating to IDVT in childhood is sparse. The possibility of IDVT should be considered when examining a child with a swollen and painful limb. Imaging should be with duplex ultrasound, followed by spiral CT to include assessment of the IVC. A thrombophilia screen should be taken prior to anticoagulation with LMWH (and warfarin). Thrombolysis should be considered in cases of extensive IDVT.*

Keywords: Paediatric; Deep vein thrombosis; Management; Anticoagulation; Thrombolysis; Thrombectomy.

Introduction

The estimated incidence of symptomatic venous thromboembolic disease (VTE) in children is 5.3/10,000 (0.05%) hospital admissions *versus* 2.5–5% for adults.[1–10] The occurrence of VTE in childhood has a bimodal distribution. The first peak is in the neonatal period (0–28 days) and is thought possibly to be due to the lower concentrations of antithrombin, heparin cofactor II and protein C along with a reduced fibrinolytic capacity, thus resulting in a prothrombotic state. The incidence then decreases significantly after the first year of life, with the second peak during puberty and on into adolescence, associated with reduced fibrinolytic activity.[11] VTE, does occur at all ages (as demonstrated in Section 2), has many well-recognised risk factors and others that are rarely considered. In this paper, we consider the evidence behind those risk factors that should be sought, the investigations best employed and treatment options in the management of iliofemoral deep vein thrombosis (IDVT) in the paediatric patient.

Case Study

A 7-year-old schoolboy presented with a 4-day history of right-sided hip and groin pain associated with a limp on that side. There was no prodromal illness of note. He had been born by normal vaginal delivery at 42 weeks and had no history of admission to Special Care Baby Unit or central venous catheterisation. Since 3 years of age, he was noted to have some autistic features and thus continues to attend a special needs school. On examination he was well with no features of systemic disease. Since, admission his right leg had become swollen (mid-thigh circumference 2.5 cm greater than left) with evidence of superficial venous hypertension (Fig. 1). It was also noted that the right testicle was absent. Examination of the hip and knee was normal. A diagnosis of proximal deep vein thrombosis was suspected and confirmed by compression duplex scan.

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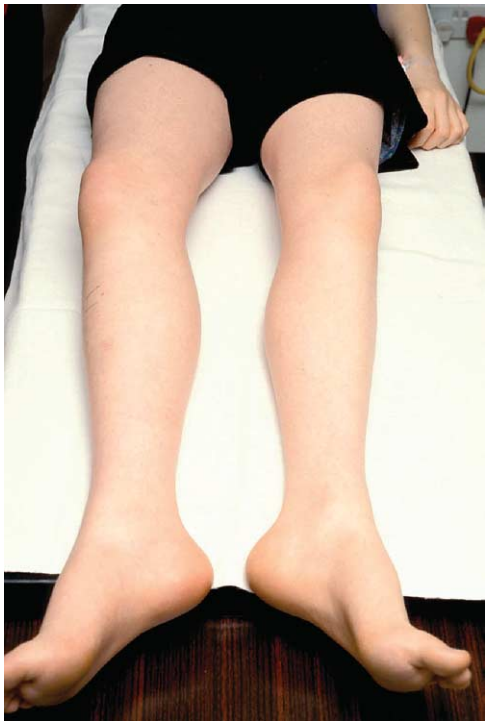

Fig. 1. Patient with swollen right leg and signs of superficial venous hypertension.

A thrombophilia screen was sent before commencing the patient on subcutaneous low molecular weight heparin (LMWH) for 2 weeks, prior to commencing warfarin. He was found to be heterozygous for factor V Leiden mutation. Compression therapy with grade I compression stockings was commenced and multi-slice CT scanning of the abdomen and pelvis was performed. This scan demonstrated an absent infra-renal inferior vena cava with the pelvic and lower limb veins draining through grossly dilated spinal and lumbar veins (Fig. 2). There was no abnormality of the solid abdominal organs. Anticoagulation with warfarin shall continue indefinitely.

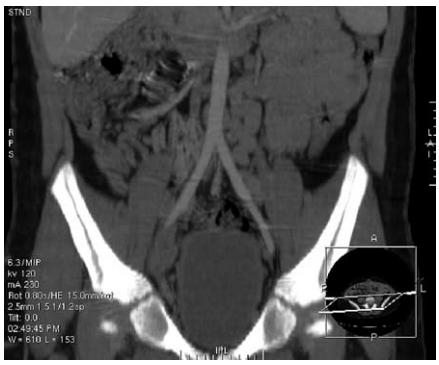

Fig. 2. CT image (unenhanced) showing absent infra-renal IVC.

Methodology

An electronic search of the literature was undertaken using search terms of 'thrombosis', 'paediatric', 'pediatric', 'childhood', 'venous', 'diagnosis', 'therapy', and 'management'. All publications pertaining to the management of IDVT in childhood were analysed and then categorised according to their level of evidence. Recommendations were then made on the basis of this.

Systemic VTE in the Paediatric Patient

The majority of VTE within the first year of life is associated with central venous access devices.[8–10,12,13] The femoral vein is rarely used for central venous access in the neonate (the majority of catheters were inserted via an umbilical vein or the upper venous system) so IDVT is rarely seen in this population. However, there have been reports of spontaneous thromboses in the visceral veins of neonates, but these have been linked to factors such as sepsis, dehydration, perinatal hypoxia, or maternal diabetes.[14]

While an age greater than 1 year seems to be protective via such postulated mechanisms as a reduced capacity to produce thrombin,[15,16] increased capacity of alpha-2 macroglobulin to inhibit thrombin,[17] and enhanced antithrombotic potential of the vessel wall,[18,19] there are increasing numbers of children older than this developing VTE as secondary complications to other underlying disorders. Approximately 95% of episodes of VTE in childhood have an underlying, serious condition as an aetiological factor causing the thrombosis. These conditions include malignancy, trauma, surgery, congenital heart disease and other malformations of the vascular system, renal disease and autoimmune diseases such as systemic lupus erythematosus (SLE).[8,20–22] The important acquired and congenital risk factors associated with VTE are shown in Tables 1 and 2, respectively.

The role of congenital prothrombotic states in the aetiology of VTE remains controversial. There is good evidence that the defects affecting the physiological anticoagulant system (i.e. factor V Leiden mutation, factor II variant G20210A, and deficiencies in proteins C and S, and antithrombin) can play a causal role in thrombotic events.[23,24] Metabolic diseases such as hyperhomocysteinaemia due to the homozygous methylenetetrahydrofolate reductase (MTHFR) polymorphism C677T, homozygous homocystinuria, and increased concentrations of lipoprotein (a) have been shown to increase the risk of both arterial and venous thromboembolism.[23–28]

Table 1. Acquired risk factors associated with paediatric VTE[49]

Perinatal diseases	Birth hypoxia/asphyxia
	Respiratory distress syndrome
	Neonatal sepsis
	Diabetic mother
	Dehydration
	Necrotizing enterocolitis (NEC)
	Polycythaemia
	Congenital nephritic syndrome
Iatrogenic cause	Central venous access devices
	Surgery
	Immobilisation
	Traction/plaster cast
	Extracorporeal membrane oxygenation (ECMO)
Acute illnesses	Trauma
	Sepsis
	Dehydration
	Nephrotic syndrome
	Acute lymphoblastic leukaemia
	Acute rheumatic diseases
Chronic illnesses	Malignancy
	Renal diseases
	Cardiac malformation
	Chronic rheumatic/autoimmune diseases
	Lupus anticoagulant
	SLE
	Antiphospholipid antibody syndrome
	Behçet's disease
	Diabetes mellitus
	Inflammatory bowel disease
	Haematological disease
	Thalassaemia
Chemotherapy/ drugs	Prednisolone
	Oral contraceptives
	L-aspariginase
	Heparins
	Coagulation factor concentrates
	Smoking

Table 2. Inherited and congenital risk factors for paediatric VTE[49]

Haematological	Common
	Factor V G1691A gene mutation
	Factor II G20210A gene mutation
	Increased apolipoprotein (a)
	Homozygous C677T polymorphism in the MTHFR gene
	Activated protein C resistance
	Rare
	Protein C deficiency
	Protein S deficiency
	Antithrombin deficiency
	Hyperhomocysteinaemia
	Very rare
	Dysfibrinogenaemia
	Plasminogenaemia
	Homozygous homocystinuria
	Probably inherited
	Increased factor VIIIC, IX, or fibrinogen
	Decreased levels of factor XII
Anatomical	Cardiac
	Venous
	Anomalous venous anatomy
	Absent IVC
	Structural
	Cervical rib

VTE in children (and adults) is a multifactorial condition. There is now level II evidence that multiple haemostatic prothrombotic defects or the association of these risk factors with environmental or clinical situations greatly increases the risk of VTE.[29,30] The relative risk of recurrent episodes of VTE is also significant and increases with the number of inherited gene defects. It has been shown that there is a 4.6-fold increased risk of recurrent VTE in children with a first spontaneous thrombosis and a single prothrombotic defect, and a documented 24-fold increased risk in those with multiple defects.[27]

Central Venous Catheter Related VTE

Central venous catheters (CVC) are placed for short-term use. They are used mostly in intensive care settings for fluid management, haemodialysis, and drug administration or for long-term supportive care for children requiring total parenteral nutrition (TPN) or chemotherapy for malignant disease. CVC-related VTE does carry a significant morbidity, including pulmonary embolus (PE)[31,32] and post-thrombotic syndrome (PTS).[33] CVC-related VTE has been divided into three types; clots at the tips of the CVC that impair the withdrawal of blood or infusion, fibrin sleeves that are not adherent to the vessel wall but occlude the catheter, and CVC-related VTE that is adherent to the vessel wall, can cause complete or partial occlusion and is, therefore, the most clinically significant.[34] While in most circumstances such catheters are placed in the jugular or subclavian vein, in the older child that is critically ill, or a younger child with a chronic condition where alternative access sites have been exhausted, the femoral vein can provide central venous access. Femoral CVC-related VTE is, therefore, an important clinical entity and needs to be considered when assessing a child with IDVT (level C recommendation).

Clinical Presentation

The clinical syndrome associated with IDVT can present to a number of specialists; most frequently paediatricians, but also vascular surgeons, orthopaedic surgeons (as in our case) and others. A multidisciplinary approach is mandatory, and will certainly require input from radiology, haematology and also other professions allied to medicine such as physiotherapy.

Deep vein thrombosis (DVT) occurs in the upper venous system in 60% of children, mostly being CVC-

Table 3. Signs and symptoms of acute IDVT

Symptoms	None
	Pain
	Immobility
	Reduced range of motion
	Swelling
	Shoe(s) not fitting
	Jewellery not fitting
	Underlying disease
	Complication
	PE
	Phlegmasia cerula dolens
Signs	Swelling
	Tenderness over affected vessels
	Venous hypertension
	Discoloured limb
	Visible superficial veins
	Underlying disease
	Complication (i.e. PE)
	Chest pain
	Shortness of breath
	Haemoptysis
	Cardiac arrhythmia

related.[10] Non-CVC-related DVT that is symptomatic occurs most frequently in the lower extremities.[35] Those DVTs affecting the proximal iliac and femoral vessels are the most clinically important, given the higher incidence of PE amongst this patient group and potential seriousness of subsequent PTS. There is a myriad of symptoms associated with IDVT and these are summarised in Table 3. The commonest presenting symptoms found in the literature were pain and swelling in the affected limb (evidence level III). The clinician must maintain a high index of suspicion of VTE when managing a child who presents with these features.

Diagnosis of IDVT

While there has been a study to assess the diagnostic investigation that best determines that location of CVC-related VTE in the upper venous system,[36,37] there are currently no studies determining the sensitivity and specificity of diagnostic testing for lower venous system CVC and non-CVC-related VTE in children. The best that can be gained is level III evidence on which one can make the level C recommendation of compression B-mode ultrasonography and duplex ultrasonography as screening tests. Venography remains the 'gold standard' test, and helical CT (with contrast) or magnetic resonance venography are useful to provide anatomical/structural data on the venous system (and other areas of interest) as well as some information about the extent of thrombus in those parts of the venous system not visualised by ultrasound (such as the pulmonary vasculature if suspicious of PE).[38] It is recommended by the authors that a cross-sectional modality is used routinely in conjunction with ultrasound and/or venography due to the limited information that the latter diagnostic methods give about surrounding structures.

Management Once IDVT is Confirmed

Alongside definitive treatment (either anticoagulation or thrombus removal by whatever mechanism), blood must be drawn for screening of pro-thrombotic risk factors as described in Table 4. It is important to stress that such testing should follow a logical, step-wise procedure and should be supervised by a haematologist (Fig. 3). It is worth pointing out at this stage that 'normal' values for these proteins and DNA assays vary for different ethnic groups, and even geographically within the same group.[39–42]

Level I and II evidence exists to support the screening of patients in a specialist anticoagulation clinic for thrombophilic defects.[12,14,25–27,43–48] There is also evidence from a study in 2001 that when thrombosis occurs in a paediatric patient in the absence of an underlying cause, the risk of recurrent VTE is also sufficiently high to justify such detailed investigation and analysis.[27]

Protein-based assays can be affected by the acute thrombotic episode and, therefore, plasma samples

Table 4. Recommended screening and re-screening for prothrombotic risk factors

Protein based assays at onset	DNA based assays at onset	Protein based assays: repeated testing
APC-resistance	Factor V G1691A	Protein C activity
Protein C activity	Factor II G20210A	Free protein S antigen
Free protein S antigen	MTHFR C677T	Antithrombin activity
Antithrombin activity	Other polymorphisms	Fibrinogen
Fibrinogen		Plasminogen
Plasminogen		Factor VIIIC, factor XII
Factor VIIIC, factor XII		Lipoprotein (a)
Lipoprotein (a)		Fasting homocysteine
Fasting homocysteine		Antiphospholipid/anticardiolipin IgM/IgG
Antiphospholipid/anticardiolipin IgM/IgG		

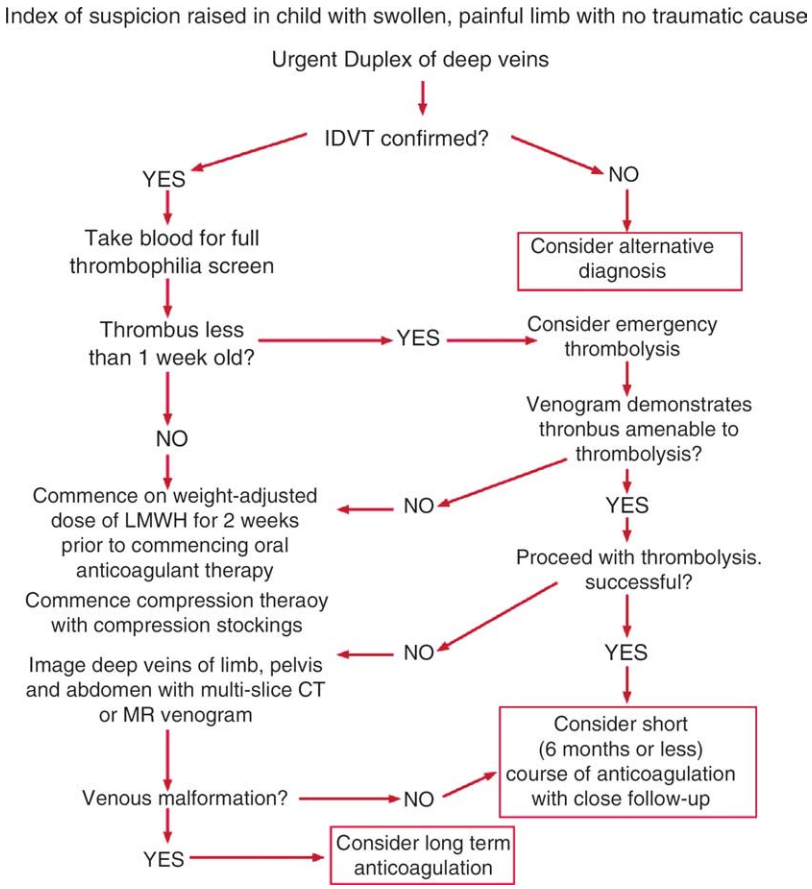

Fig. 3. Management decisions in paediatric IDVT.

should be obtained at least 3–6 months after the initial episode (recommendation level B). Oral anticoagulants may also influence protein-assays, so it is recommended that samples are drawn 14–30 days after cessation of oral anticoagulants. The situation with parenteral anticoagulants (unfractionated heparin and LMWH) is less clear, and to maintain the quality of results it is suggested that samples are taken when the patient is not receiving these drugs. DNA assays are affected neither by the acute thrombotic episode nor the administration of thrombolytic or anticoagulant agents, and can, therefore, be performed at any point after the VTE episode (evidence level III, recommendation level C).[49]

Treatment Options

The rarity of the condition has meant that there have been no large-scale, prospective trials conducted. Treatment options include anticoagulation, systemic thrombolysis (bolus and/or infusion), local/catheter-directed thrombolysis and thrombectomy. Analysis of the literature would suggest that treatment strategies vary greatly between, and even within institutions.

While the general approach to paediatric thrombosis is the same as adults, the differences in underlying aetiology, age related variations in the clotting system and technical differences may affect the choice of treatment method.

Antithrombotic therapy in children

Heparin

Unfractionated heparin (UFH) remains a commonly used anticoagulant in paediatric patients. A tertiary referral centre for paediatrics reported up to 15% of inpatients were exposed to UFH each day.[50]

Mechanism of action. The main anticoagulant activities of heparin are mediated by the catalysis of antithrombin (AT) and can be impaired by low plasma levels of this protein. Physiologically low levels of AT (<0.30 U/ml) are found from birth to $\sim$3 months of age,[51–53] and can be even lower in acute disease states.[53,54] Heparin inactivates specific coagulation

Table 5. Protocol for administration and adjustment of systemic (IV) unfractionated heparin in children[58]

Stage	Description	aPPT (s)	Bolus (U/kg)	Stop infusion (min)	Rate change (%)	Repeat aPPT
I	Loading dose		75 IV over 10 min			
II	Initial maintenance dose					
	Infants <1 year		28/h			
	Children >1 year		20/h			
III	Adjustment*	<50	50	0	+10%	4 h
		50–59	0	0	+10%	4 h
		60–85	0	0	0	Next day
		86–95	0	0	−10%	4 h
		96–120	0	30	−10%	4 h
		>120	0	60	−15%	4 h
IV	Obtain blood for aPTT, check 4 h after heparin loading dose and 4 h after every change in infusion rate					
V	When apt values are in therapeutic range, perform daily FBC and aPTT measurement					

* Heparin adjusted to maintain aPTT at 60–85 s, assuming that this reflects an anti-FXa level of 0.35–0.70.

enzymes (in particular thrombin) through its action on AT.[55]

Therapeutic range. The therapeutic range for the treatment of VTE in adults is an aPTT corresponding to a heparin volume by protamine titration of 0.2–0.4 U/ml or an anti-FXa level of 0.35–0.7 U/ml.[56] Unfortunately, aPTT ranges are universally calculated using adult plasma and extrapolating these ranges to a paediatric patient group is of unknown validity. Also children have a higher baseline aPTT, so any increase in this value represents a reduced relative increment when compared to similar changes in the adult population. However, aPTT values in paediatric patients correctly predict therapeutic heparin doses in about 70% of cases.[57]

Dose and monitoring. The dose of heparin required in paediatric patients to achieve adult therapeutic aPTT values has been assessed in a prospective cohort study using a weight-based normogram. Bolus doses of 75–100 U/kg result in therapeutic aPTT values in 90% of children. Maintenance doses are age-dependent and can be seen in Table 5. As in adults, dose adjustment of IV UFH in paediatric patients is challenging, but a validated method is demonstrated also in Table 5.

Low molecular weight heparins

LMWHs have quickly become the treatment of choice for paediatric VTE, despite the lack of data supporting their efficacy in these indications. Advantages of these drugs include a reduced need for monitoring (especially useful in a child) and a reduced incidence of side effects associated with UFH such as heparin-induced thrombocytopaenia (HIT), osteoporosis and drug interaction. Perhaps due to altered plasma binding characteristics, weight-adjusted doses appear to be less predictable when compared to adult groups.[55,58]

Mechanism of action. At similar anti-FXa concentrations, UFH inhibits free-thrombin generation to a greater degree than does LMWH in neonates, children and adults. Studies *in vitro* show thrombin generation is similar in adults and children at the same concentration of LMWH. Further work demonstrated at a LMWH concentration of 0.25 U/ml thrombin generation was delayed and reduced by approximately half in newborns compared to adults. The observed differences were matched by reciprocal reductions in the rates of prothrombin consumption.[59]

Therapeutic range. In a situation similar to UFH, doses of LMWH have been extrapolated from adult studies, and are centred on anti-FXa levels. Evidence would suggest that anti-FXa levels of 0.5–1.0 U/ml measured in a sample drawn 4–6 h post-subcutaneous injection indicates a therapeutic dose of LMWH. Dosing guidelines are shown in Table 6.

Monitoring. Once a therapeutic dose has been achieved, the need for ongoing monitoring has yet to be established in a paediatric population.

Warfarin and other vitamin K antagonists (VKA)

These drugs function through inhibiting hepatic production of the vitamin K-dependent factors in the clotting cascade (II, VII, IX and X). In neonate, these clotting factors are decreased to levels similar to adults on therapeutic doses of warfarin. The problems of VKA administration in newborns, and some older children, are manyfold. Formula milk contains high levels of vitamin K (to prevent haemorrhagic disease of the newborn) and as such babies fed this way are

Table 6. Dosing guidelines for LMWH in treating paediatric patients with VTE[58]

Drug	Initial treatment dose	Initial prophylactic dose
Enoxaparin		
Age-dependent dose (mg/kg b.d.)		
<2months	1.5	0.75
>2 months	1.0	0.5
Dalteparin		
All age paediatric dose (U/kg o.d.)	129±43	92±52
Tinzaparin		
Age-dependent dose (U/kg)		
0–2 months	275	
2–12 months	250	
1–5 years	240	
5–10 years	200	
10–16 years	275	
Reviparin		
Weight-dependent dose (U/kg b.d.)		
<5 kg	150	50
>5 kg	100	30

relatively VKA-resistant. Conversely, breast milk contains low concentrations of vitamin K, and subsequently breast-fed babies are VKA sensitive.[60,61]

VKAs are also only available in tablet form, and while they can be dissolved in water, there are no validated safety and efficacy data for this mode of administration. Monitoring is perhaps the most important and challenging issue. Frequent assessment of the INR is required, due to changes in diet, medications and plasma concentrations of the vitamin-K dependent factors. Venous access soon becomes troublesome in this sub-group of patients.

Therapeutic range. Current therapeutic INR ranges for children are extrapolated from adult studies because no clinical trial has assessed the optimal INR range for paediatric patients based on clinical indication or outcome. A protocol for dosing warfarin (and the other VKAs) is shown in Table 7.

Thrombolytic agents

The evolution of treatment for intra-arterial thrombosis in adult populations, especially during myocardial infarction, saw the arrival and subsequent development of a range of 'clot-busting' drugs. These novel treatments then enjoyed a wider range of clinical applications including treatment of VTE. The route of administration has also been studied in the adult setting, with the options being systemic or local/catheter-directed thrombolysis (CDT). While one study supports the use of CDT in adult occlusive iliofemoral DVT, there are no studies that compare the efficacy, safety, or cost of different thrombolytic agents in children.

Mechanism of action. The actions of thrombolytic drugs are mediated by converting endogenous plasminogen to plasmin. At birth there are decreased levels of plasminogen (about 50% adult values, or 21 mg/100 ml)[51,52] which slows the production of plasmin[62] and thus reduces the thrombolytic effect of streptokinase (SK), urokinase (UK), and tissue plasminogen activator (tPA).[63]

tPA is the agent of choice in the paediatric setting. The reasons include improved clot lysis in an *in vitro* study when compared with SK and UK, lower immunogenecity, greater fibrin specificity and, historically, less (theoretical) risk of virus transmission.[64,65] tPA is more expensive than other thrombolytic agents and no clinical trial has supported the *in vitro* data suggesting enhanced clot lysis over and above SK and UK. tPA has, perhaps, the strongest evidence-base in the current literature, although there have been institutional reports of experience using both SK and UK. The optimal use, dosage, efficacy, and bleeding toxicity of tPA thrombolysis in children are unknown. Currently, anticoagulation using UFH or LMWH constitutes standard therapy for children with thrombosis.[10] However, paediatric haematologists are

Table 7. Protocol for dosing paediatric patients with VKA—to maintain an INR 2–3[58]

Stage	INR	Action
I		
Day 1	1.0–1.3	0.2 mg/kg orally
II		
Days 2–4	1.1–1.3	Repeat day 1 loading dose
	1.4–1.9	50% of day 1 loading dose
	2.0–3.0	50% of day 1 loading dose
	3.1–3.5	25% of day 1 loading dose
	>3.5	Hold dosing until INR<3.5, then restart according to stage III guidelines
III		
Maintenance	1.1–1.4	Increase by 20% of dose
	1.5–1.9	Increase by 10% of dose
	2.0–3.0	No change
	3.1–3.5	Decrease by 10% of dose
	>3.5	Hold dosing until INR<3.5, then restart at 20% less than last dose

regularly asked about the use of tPA in a growing number of children who present with a wide variety of thrombi. Interest in tPA is due to the recognition that successful thrombolysis is associated with more rapid and complete restoration of blood flow and less tissue infarction.[66] Thrombolytic therapy has been shown to be more efficacious than anticoagulation alone in adults with pulmonary embolism[67] and acute coronary thrombosis[68] and for prevention of post-thrombotic syndrome (PTS) secondary to IDVT.[69] Children exhibit low rates of death, pulmonary embolism, thrombus propagation, thrombus recurrence, or bleeding toxicity with anticoagulant therapy. PTS, a clinical spectrum of swelling, pain, skin changes, and stasis ulcers that occurs as a sequela to obstructed venous flow, has been reported in 10–20% (and in one series 60%) of children with venous thrombosis.[8,9,70,71]

Dose and route of administration. There is a large variation in reported tPA doses in children, with many recommendations being transferred from the treatment of arterial thrombosis. In the paediatric population, the local dose of tPA has varied from 0.01 to 0.5 mg/kg/h and infusion times from a few hours to 30 days.

A prospective study using 0.5 mg/kg/h systemic tPA for 6 h concurrently with heparin (10 U/kg/h) and FFP supplementation (to augment its effects) prior to tPA infusion reported complete clot lysis in 13 of 20 patients (65%) [arterial thrombosis, 12 patients; venous thrombosis, one patient], partial resolution in four patients (20%) [arterial thrombosis, one patient; venous thrombosis, three patients], and no response in three patients (15%) [arterial thrombosis, one patient; venous thrombosis, two patients].[72] Another study used a dose of 0.5 mg/kg/h for the first hour followed by 0.25 mg/kg/h until complete resolution occurred or the infusion was complicated by bleeding. Complete clot lysis was achieved in 16 of 17 patients within 4–11 h.[73] Wang *et al.* performed a study looking at low-dose administration of tPA. Thirty-five children were treated with either standard or low-dose infusions of tPA.[74] Results were complete thrombolysis of 28 of 29 (97%) acute thrombi, while all six chronic thrombi had a partial response. In contrast to the recommended adult-derived dosages of 0.1–0.5 mg/kg/h, the authors found that initial doses of less than 0.01 mg/kg/h were effective in 12 of 17 patients with acute thrombosis. Neonates required 0.06 mg/kg/h. Major bleeding occurred in only one extremely preterm infant. Minor bleeding, primarily oozing at intravenous sites, occurred in 27% of children during tPA infusions. Prophylactic UFH or LMWH was infused concomitant with tPA in 42% of the children and did not increase the risk of bleeding.

No data exist comparing the outcome of local and systemic thrombolytic therapy in paediatric patients making it impossible to suggest that there is an advantage in either when treating children with IDVT.[75] There is also a theoretical risk that the small vessel size in children may increase the risk of local vessel injury with new thrombus subsequently forming. In CVC-related VTE local therapy it would seem most appropriate if the thrombolytic agent was delivered via the catheter already *in situ*. There are no reports of pulse-spray CDT in children.[58] A guide to doses of thrombolytic agent is shown in Table 8.

Adverse events. Technical problems with catheter positioning (secondary to thrombus location and patient size), vessel rupture, and local and distant bleeding are potential complications of this procedure.[76] A recent review of the literature determined that bleeding complications requiring packed red cell transfusions occur in 20% of children receiving tPA thrombolysis.[77] Weiner *et al.* reported intracranial

Table 8. A guide to thrombolytic therapy for paediatric patients[58]

Treatment	Single-lumen CVC	Double-lumen CVC	SC port
Local instillation tPA			
<10 kg	0.5 mg diluted in 0.9% NaCl to required volume to fill line	0.5 mg per lumen diluted in 0.9% NaCl to fill volume of line; treat one lumen at a time	0.5 mg diluted with 0.9% NaCl to 3 ml
>10 kg	1.0 mg in 1.0 ml 0.9% NaCl; use amount required to fill volume of line to maximum of 2 ml=2 mg	1.0 mg/ml; use amount required to fill volume of line to maximum of 2 ml=2 mg per lumen; treat one lumen at a time	2.0 mg diluted with 0.9% NaCl to 3 ml

Treatment	Loading dose	Maintenance dose	Monitoring
Systemic thrombolytic therapy			
Urokinase	4400 U/kg	4400 U/kg/h for 6–12 h	Fibrinogen, TCT, PT, aPTT, FBC
Streptokinase	2000 U/kg	2000 U/kg/h for 6–12 h	Fibrinogen, TCT, PT, aPTT, FBC
Tissue plasminogen activator (tPA)	None	0.1–0.6 mg/kg/h for 6 h	Fibrinogen, TCT, PT, aPTT, FBC

Heparin should be commenced during, or immediately after completing thrombolytic therapy. A loading dose may be omitted. TCT, thrombin clotting time; PT, prothrombin time; FBC, full blood count.

haemorrhage in two of seven neonates receiving tPA.[78] A perception of increased tPA-associated bleeding has limited the use of thrombolysis in children, and a recent report with standard doses (0.5 mg/kg/h average dose) also revealed significant bleeding complications.[65] Due to the inherent risk of thrombolytic agents, anticoagulation alone should be considered for cases of thrombosis with non-urgent sequelae.

Thrombectomy and other surgical therapies

Surgical thrombectomy is rarely used as treatment in children. The common situations in which thrombectomy is reported include IVC thrombosis associated with intra-vascular extension of Wilm tumour, acute thrombosis of Blalock–Taussig shunts, life-threatening intra-cardiac thrombosis immediately after complex cardiac surgery, prosthetic valve thrombosis, and peripheral arterial thrombosis secondary to vascular access in neonates. While there are no guidelines on the use of surgical thrombectomy (specifically in IDVT) there is consensus that in many situations the risk of VTE recurrence secondary to vascular damage remains high. The risk/benefit balance must be considered on each case's merits: where there is threatened loss of life or limb surgical intervention may be justified.[58]

Several different percutaneous methods of thrombus removal are available and use a variety of devices. These include direct aspiration (using suction or hydrolytic action) and mechanical disruption (with spinning blades).[79] Some investigators are also assessing the possibility of clot lysis using ultrasound.[80] Depending on its mode of action the catheter aspirates, macerates or fragments the thrombus as it is advanced through the vessel. Residual thrombus may be treated with low-dose, short duration thrombolysis.[81] As thrombectomy will only clear large vessels thrombolysis may be required to clear smaller vessels and restore tissue-level perfusion.[79] There is no study-derived evidence to support the use of any of these devices in children.

Vena cava filter device

While the authors realise that this is not a direct treatment for IDVT, it may prove a useful adjunct. IVC (or less commonly SVC) filters may be placed in patients who are at high risk of PE. The filters, of many different designs, essentially act as a trap mechanism for thrombus fragments travelling in the vena cava that would otherwise embolise to the lung. Indications for use would include patients in whom anticoagulation or thrombolysis is too high risk (e.g. prior intra-

Table 9. Management decisions in paediatric IDVT: evidence and recommendation levels

Management step	Evidence level	Recommendation level
Clinical presentation		
History/signs of painful, swollen limb with signs of superficial venous distension	III	C
Imaging of thrombosis		
USS/duplex as screening tool in upper limb	Ib	A
USS/duplex as screening tool in lower limb	III	C
Lineogram/venogram	Ib	A
CT/MR venogram	3	C
Diagnosis of underlying thrombophilia		
Full prothrombotic screen by specialist laboratory at first presentation	I/II	B
Diagnosis of underlying venous/structural anomaly		
CT	III	C
MR	III	C
Use of heparins for 5–10 days for simple DVT		
UFH	I	A
LMWH	I	A
Use of heparins for prolonged period for extensive DVT		
UFH	I	B
LMWH	I	B
Six month administration of warfarin/VKA in first VTE	II	C
Thrombolysis		
Should not be used routinely	II	C
Vena cava filter device		
If patient at high risk of PE (i.e. contraindication to anticoagulation, PE on full anticoagulation, extensive/proximal DVT)	III	C

ventricular haemorrhage) or have had break through PE when fully anticoagulated.

There is limited experience in the use of filters in children, with only a few case reports discussing placement and follow-up.[82–84] Many technical questions remain unanswered with regard to device selection, duration of placement and overall safety and efficacy. It is the most experimental of all those therapies in children discussed here, and does carry some associated morbidity. Complications include migration, vessel perforation and thrombosis.

A summary of the management steps in treating a child with acute IDVT, with evidence and recommendation levels, is illustrated in Table 9.

Conclusion

Level I evidence relating specifically to the treatment of IDVT in children is sparse, with current practice a result of extrapolating from adult medicine or an institution's or individual clinician's preference. With more episodes of paediatric VTE occurring and being recognised, there is a need for greater consensus and basic treatment guidelines.

Multiple factors, both genetic and acquired, contribute to thrombosis in children. It appears that children who are heterozygous for one or more risk factor or who have an acquired defect (either haematological or structural) are at an increased risk of VTE. Both the coagulation system and venous anatomy must be examined using techniques that have been discussed in this paper.

The first-line treatment of IDVT is UFH or LMWH to prevent extension, followed by long-term anticoagulation with a VKA to prevent recurrence. Early experience suggests tPA thrombolysis may be safe and effective in children with IDVT, if the diagnosis and treatment is instituted within 14 days of the event. After this period, experience in adult medicine at least, has shown that the risk/benefit ratio favours conservative therapy.

As awareness of IDVT and other venous thromboembolic diseases grows, it may be possible to create prospective, international registries or randomized studies that will enable us to make stronger evidence-based treatment recommendations.

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Accepted 28 November 2005
Available online 3 February 2006