

Review Article

Thrombosis in Children: Current Perspective and Distinct Challenges

Matthew W. Richardson [1,*], Geoffrey A. Allen [1, 2], Paul E. Monahan [1, 2]

[1]Department of Pediatrics, and [2]Center for Thrombosis and Hemostasis, University of North Carolina at Chapel Hill, USA

Keywords

Thrombosis, child, neonate, hemostasis, anticoagulation, thrombophilia

Summary

Coincident with a true increase in the incidence of thrombosis in childhood has come an appreciation of the impact of thromboembolic events upon children. In part, the greater awareness of childhood thrombosis reflects improved diagnostic imaging, which allows more sensitive identification of clots in infants and children. At the same time, advances in supportive care have meant that more children are being exposed to, surviving and living with thromboembolic risk factors and complications than previously. Because data regarding pediatric thrombosis have been lacking, treatment strategies have been extrapolated from experience in adults. This approach, however, results in diagnostic and therapeutic pitfalls. An understanding of issues unique to pediatric thrombosis is required; recent insights and the ongoing challenges are reviewed.

Epidemiology of Thrombosis and the Developing Coagulation and Fibrinolytic Systems throughout Childhood

Thrombosis in children, although increasingly common, is still a rare event in comparison to thrombosis in adults. The Canadian Registry of Venous Thromboembolic Complications in Children reported an incidence of 0.07/10,000 pediatric population (1) (5.3/10,000 hospitalized children) in contrast to an estimated incidence of 2.5 to 5% of adults (2). Several factors likely contribute to the low incidence of thrombosis in children. Certainly the unique hemostatic physiology of the infancy and childhood, as detailed below, has an impact. Also important is the integrity of the vessel wall and its influence on thrombosis. The vascular endothelium of children has not accumulated damage from diseases such as hypertension, diabetes, or hypercholesterolemia, and so maintains anticoagulant properties. Similarly, the majority of children have not been exposed to acquired thrombotic risk factors, such as oral contraceptives, smoking, antiphospholipid antibodies, or malignancies.

Although components of the coagulation system appear as early as ten weeks gestational age in the human fetus, the development of this system is incomplete at birth and is dynamic throughout childhood. Evaluation of coagulation factor values in children requires attention to normal ranges for age, and established normal ranges for fetal, neonatal and childhood ages are now published (3-5). Trends in representative factors are shown in Figs. 1-3, demonstrating the differences in coagulation profiles of the neonate, the older child, and the adolescent transitioning to an adult hemostatic profile. Components of the coagulation system do not cross the placenta from the mother into the infant. Differences from adult values do not represent merely immature protein synthetic ability, as a number of factors are present at adult levels (e.g. fibrinogen, factor V, factor VIII, factor XIII) or greater than adult levels (e.g. alpha-2 macroglobulin, PAI1) in childhood. One mechanism possibly protecting neonates and children from thromboembolic events, when compared to adults, is a decreased potential for thrombin generation. Levels of the vitamin K-dependent clotting factors, as well as most contact factors, are strikingly low in term infants (Fig. 1). In term and preterm infants thrombin generation is lower than at any other point in life, resulting in delayed and decreased thrombin generation, similar to plasma from anticoagulated adults (3). In contrast, the co-factors V and VIII and fibrinogen are not significantly different from adult levels at birth. Despite sharp increases to within adult normal ranges in the first 6 months of life, mean prothrombin and factors VII, IX, and X remain significantly below mean adult levels through childhood (6, 7). Pooled plasma from children aged 1-16 years, compared to adult plasma, showed 27% less thrombin generation in aPTT-based assays (8).

In addition to the decreased potential for thrombin generation, possible mechanisms to explain the decreased thrombotic risk in childhood might include inhibition of thrombin, increased fibrinolysis, or alterations in the platelet/vessel wall interaction. The lower risk of thrombosis in childhood does not appear to result from enhanced inhibition of thrombin. Antithrombin (AT), protein C, and heparin co-factor II (HC II) levels are low at birth. Protein C and HC II remain significantly low until adulthood is reached. Low total protein S antigen levels in the first half year of life likely have little impact, because adult levels of free protein S are present throughout childhood (4, 6, 9). Despite lower levels of antithrombin in the first six months of life, the activity of heparan sulfate and other glycosaminoglycans (GAGs) on endothelial cells

* Current Address: Bay State Medical Center, Pediatrics Hematology/Oncology, 3400 Main Street, Springfield, MA 01101, USA

Correspondence to: Paul E. Monahan, MD, CB#7220, 418 MacNider Bldg, UNC-CH School of Medicine, Chapel Hill, NC 27599, USA – Phone: 919-843-4984; Fax: 919-966-0907; E-mail: Paul_Monahan@med.unc.edu

Following the submission of this manuscript, the Subcommittee for Perinatal and Pediatric Thrombosis and of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) generated two relevant communications, published in the July, 2002 issue of *Thrombosis and Haemostasis*. While the positions communicated, entitled "Laboratory testing for thrombophilia in pediatric patients (117)" and "Recommendations for tPA thrombolysis in children (118)" do not conflict with this manuscript, they will be of interest to the reader.

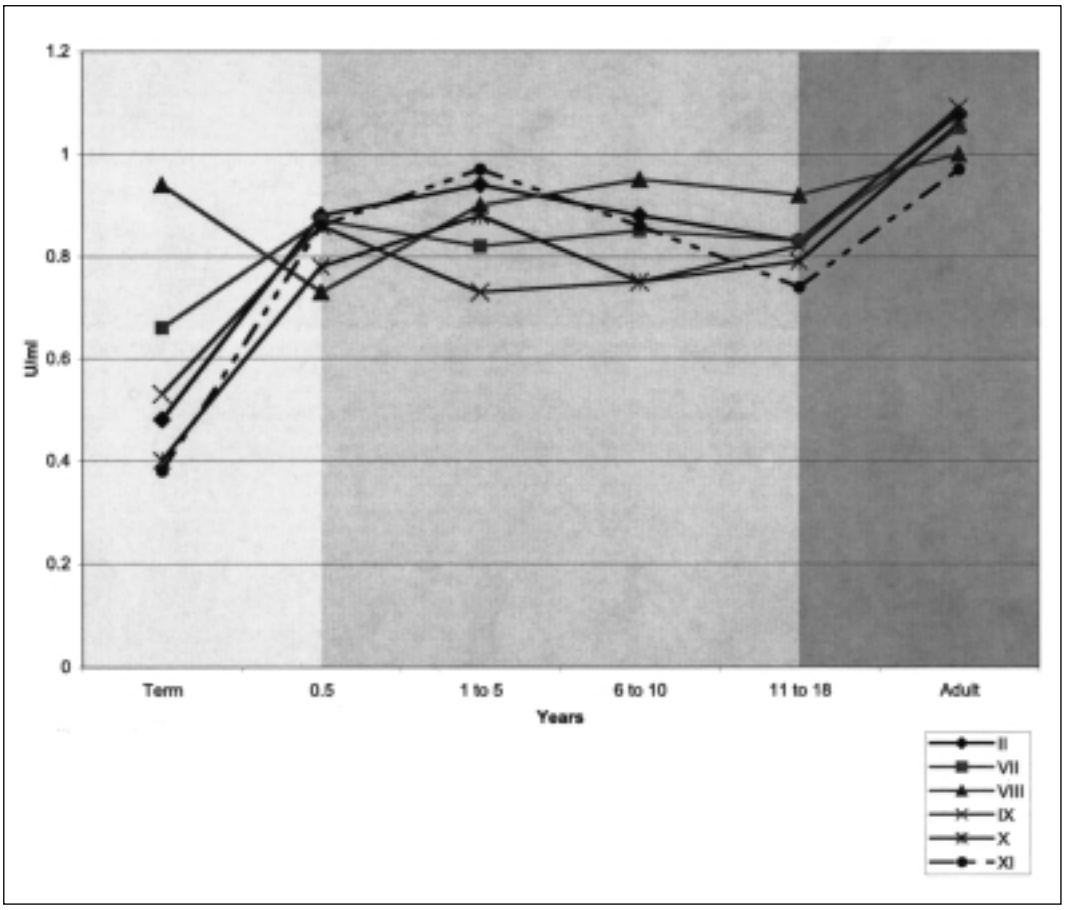

Fig. 1 Development of coagulation factors during childhood. Plasma concentrations of selected contact, vitamin K-dependent, and co-factors of coagulation over age through childhood (4, 6, 113, 114). It is useful to think of the major changes as occurring in three periods: from birth through the first 6 months of life; from the first year until early adolescence; during or by the end of adolescence

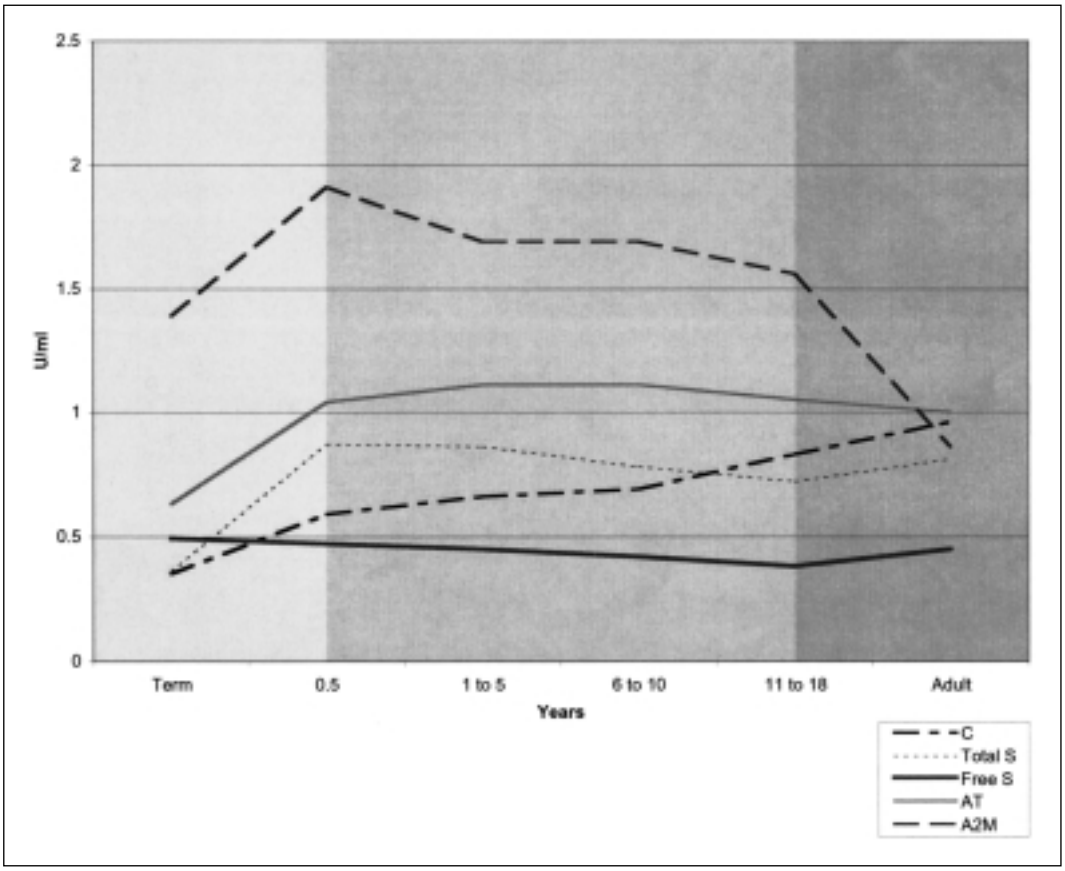

Fig. 2 Mean levels of selected antithrombotic factors in childhood. Plasma concentrations of selected antithrombotic factors over age through childhood (4, 6, 9, 113, 114)

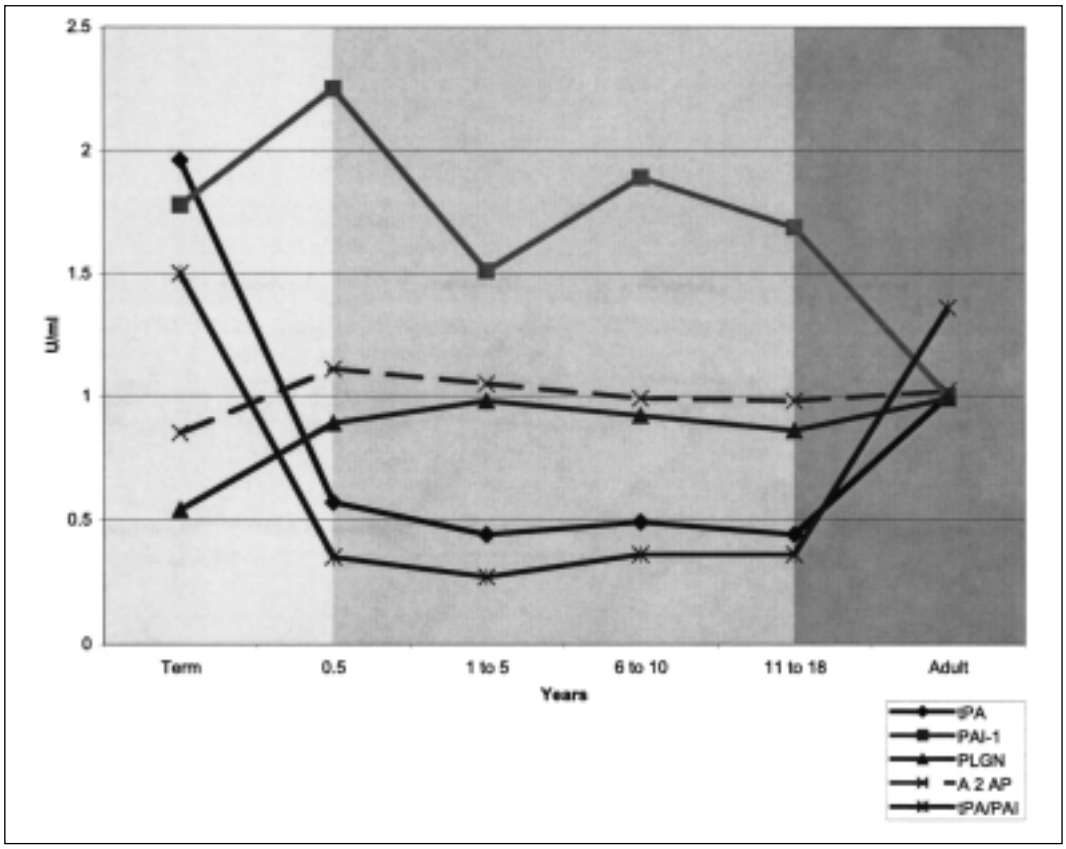

Fig. 3 The fibrinolytic system throughout childhood. Plasma concentrations of selected fibrinolytic factors over age through childhood (6, 115)

appears to be increased, which along with increased concentration of alpha-2 macroglobulin, potentiate antithrombin inhibition of thrombin generation (10). This inhibition is augmented in infancy by high levels of alpha-2 macroglobulin, an inhibitor which peaks in the first six months of life and remains elevated throughout childhood.

Protection from thrombosis in the neonate and child does not result from increased fibrinolytic activity. Although tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI-1) are each transiently elevated by the birth process, plasminogen is decreased through the first six months of life. Thereafter, levels of plasminogen and alpha2-antiplasmin approximate adult values. However, low levels of tPA and high levels of PAI-1 and alpha2-macroglobulin likely explain the decreased fibrinolytic potential described in infants and adolescents (6, 11, 12).

The role of platelet/vessel wall interactions in protection from thrombosis has been difficult to assess. Research and clinical study of platelet function in infants is challenged by the large volumes of blood required for classical platelet aggregation studies and the difficulty standardizing bleeding time testing in children. Neonatal platelet aggregation in response to epinephrine, collagen, and thrombin appears to be decreased (13); reports of differences in response to other agonists are less consistent. The decreased responsiveness does not result from differences in platelet collagen receptor GPIa/IIa, as this and other GP receptors are present in adult numbers (14). Animal studies suggest that vessel wall GAGs may enhance antithrombin activity in neonates (10) Conversely, the vessel wall of the newborn, when stimulated, may express more tissue factor than adult endothelium (15). In addition, the first three months are characterized by higher concentrations of vWF, increased vWF collagen-binding activity, and unusually large multimers of von Willebrand factor capable of more potent promotion of aggregation. The bleeding time is shorter in infants than in adults. Whole blood flow cytometric studies may identify significant differences in platelet reactivity that could not be appreciated with earlier methods (13, 16).

Factors Unique to Childhood Thrombosis

When clots do occur in childhood, at least one thrombotic risk factor is identified in the majority of children. Idiopathic thrombosis occurs in less than 10% of cases of thromboembolism in most pediatric series, compared to approximately 40% of adult thromboses (17-20). An exception is arterial ischemic stroke (AIS) in the pre- or perinatal period, which may be clinically silent, and is idiopathic in one third of cases (21-24). Most children with thrombosis have a serious underlying illness (e.g. cancer, congenital heart disease, nephrotic syndrome) and usually one or more other risk factors, either acquired or congenital (e.g. central line or a hereditary prothrombotic condition) (1, 25). This requirement to have multiple risk factors that lead to abnormal clotting is characteristic of pediatric thrombosis.

One risk factor in particular is so much more common in pediatrics than in adults that it merits special mention: the presence of a central venous line (CVL). CVLs are the most common risk factor for thromboembolism in children, associated with up to 60% of pediatric blood clots and up to 90% in newborns (17, 26, 27). The high frequency of thrombosis in the upper venous system in pediatrics is explained by the typical placement of CVLs in this location in children. Consequently, 60% of DVTs that occur in children and up to 80% occurring in neonates are in the upper venous system, compared to only 2% of adult DVTs (17, 26, 28).

Neonates

Neonatal thrombosis exhibits several characteristics that make it unique even among pediatric clotting. Although the neonatal period

spans only 4 weeks (age 0–28 days) it constitutes the single largest group of children with thromboses – approximately 12% of all pediatric clots occur in neonates (17). Prospective studies have found clinically apparent thrombosis (excluding stroke) in 2.4/1,000 neonatal intensive care unit admissions (27) and an incidence of symptomatic thrombosis of 5.1/100, 000 births (29).

The perinatal period carries relatively higher risks of systemic infection, dehydration, and perinatal asphyxia (27, 29), all of which are in turn risk factors for thrombosis. Treatment for all of these conditions usually requires a CVL for adequate access in a small, critically ill baby, which further compounds the risk for thrombosis.

Catheterization of the umbilical vessels is a risk factor unique to neonates. Thrombi have been found radiographically in up to 29% of neonates with umbilical venous catheters (UVCs) (30). The frequency of arterial thrombosis from umbilical artery catheterization has been estimated widely between 9-28% based on autopsy reports; several angiographic studies have reported rates near 30% (3).

Homozygous deficiencies of protein C, protein S and ATIII clearly present with thrombosis as early as the newborn period. What is less clear is the relative contribution of the common heterozygous hereditary coagulation defects (e.g. factor V Leiden, prothombin G20210A) to neonatal thrombosis. The diagnosis of these disorders requires large volumes of plasma from untransfused patients, a significant limitation in preterm and term infants, in whom the total blood volume may be only 80–240 cc. One prospective study found hereditary coagulation defects in seven of 35 cases of neonatal thrombosis (29).

Spontaneous renal vein thrombosis (RVT) is another problem seen more frequently in newborns than in older children. These clots are unilateral 75% of the time. In term infants, RVT often presents within the first two days of life with hematuria, proteinuria, thrombocytopenia, and a palpable abdominal mass (29, 31, 32). Preterm infants (< 37 week gestation) tend to present later.

Stroke in the neonate, both sinovenous thrombosis (SVT) and arterial ischemic stroke (AIS), has been the subject of several recent clinical studies and reviews (33-37), which demonstrate features that distinguish stroke in this age group from that in older children and adults. Although the overall incidence of SVT in childhood is 0.67 per 100,000, the incidence in newborns is 41 per 100,000 (34); the incidence of perinatal/neonatal arterial ischemic stroke is at least 7-8 times the rate 2-3/100,000 seen in older children (38). The most common presentations of neonatal stroke are seizures and lethargy; while more than half of non-neonates with SVT and AIS have focal neurologic deficits or hemiparesis, neonates present with these signs only one quarter of the time, or less (34, 38). The occurrence of perinatal stroke often goes unrecognized until neurologic deficits become obvious with motor development in the first year of life (35).

Children

While children age 1 month to 10 years old account for about 50% of all pediatric thrombosis, a quarter of these occur in the 2nd to 12th months of life (1, 17). No single year between ages 3-10 amounts to more than 5% of pediatric thromboses. Low thrombosis rates reflect the unique hemostatic profile of this age group as well as the relative absence of risk factors. Children in this age group who do develop thromboses almost always have one or more identifiable risk factors, the most common being the presence of a CVL (17). Other risk factors in this group are hematologic malignancies, cardiac disease, surgery, and infection; although independent risk factors, risk with each of these conditions is often compounded by the requirement for a CVL for treatment.

Acute Lymphoblastic Leukemia (ALL), the most common childhood malignancy in this age group, is an especially significant risk for thrombosis for many reasons. First, virtually all patients receive a CVL for the treatment of their disease. Second, L-asparaginase, a drug essential in the treatment of ALL, particularly decreases baseline amounts of ATIII compared to other components of hemostasis (3). A historical review (3) of the large studies of children with ALL receiving L-asparaginase demonstrates a median incidence of thromboembolism of 2.6% (range:1.1-14.3%). The same rate (2.8%) was found in a recent prospective study in ALL (39). Symptomatic thromboembolism in these studies occurs most often in the CNS, or at the site of a CVL. Radiographic (largely asymptomatic) CVL-related thromboses have been demonstrated in 7.3-50% of childhood cancer patients (40-42). Although silent thromboses can become manifest after removal of the CVL (41), adequate studies are lacking to direct thrombosis prophylaxis or treatment in this setting.

Complex congenital heart disease that requires cardiac catheterization for diagnosis or treatment is yet another risk factor in young children. The incidence of symptomatic thrombotic complications from cardiac catheterization without prophylactic heparinization is approximately 40% (43). Even with the use of prophylactic heparin thromboses can occur in 4–32% of procedures (43, 44).

Although a complete review of pediatric ischemic stroke is beyond the scope of this review, some aspects are worth noting. In contrast to a lower association of thrombophilic conditions with adult stroke, 30-38% of children presenting with cerebral thromboembolic disease outside of the perinatal period demonstrate prothrombotic disorders, the most commonly documented abnormalities being the presence of an antiphospholipid antibody (APLA), defects of activated protein C resistance (including factor V G1691A) and elevated lipoprotein(a) (23, 35, 36, 45-47). There is also epidemiologic evidence that recent infection with varicella imparts a risk for arterial ischemic stroke (48, 49). Despite all of the known risk factors for ischemic cerebrovascular accidents, approximately 1/3 of cases remain idiopathic (21-24).

Adolescents

After neonates, children age 11–18 years represent the next largest cohort of children with clots. About 50% of pediatric thromboses occur in this age group (1, 17). This rise in thrombosis coincides with a coagulation profile that is in transition to the adult state, including an increased potential to generate thrombin, a drop in the coagulation inhibitor alpha-2-macroglobin, and increases in acquired risk factors such as APLAs, smoking, and estrogen-containing oral contraceptives.

Diagnostic Studies

Imaging

Documentation of thrombosis in children presents its own set of difficulties. As in adults, the venogram is considered the gold standard for the diagnosis of pediatric deep venous thrombosis (50, 51). Obtaining the peripheral venous access needed for venography in a small child frequently makes the study impractical if not impossible. For this reason ultrasound is often used as the initial imaging study for DVTs of the lower extremity and "distal" upper system (i.e. veins of the neck, axillae, and arms). Several factors unique to pediatrics, however, may interfere with the test – small diameter vessels, low pulse pressure, and the likely presence of a CVL at the site of a thrombus can make compression of the vein in question difficult and the result hard to

interpret (33). If an ultrasound result is negative or equivocal and the clinical suspicion for a clot is high, a venogram should be obtained. Diagnosis of DVT of the intrathoracic upper system (proximal subclavian, innominate, superior vena cava) requires a venogram because of the low sensitivity of ultrasound for detecting clots in this region (52, 53). A prospective comparative evaluation of venography versus ultrasound for diagnosis of asymptomatic deep vein thrombosis in the upper venous system highlights the reality that there is no single gold standard for evaluation of this region. Evaluation with either test alone had a sensitivity of < 80%, and the combination of both tests is required for accurate screening and evaluation of the upper venous system (51).

Pulmonary angiography is the gold standard for diagnosing pulmonary embolus in adults, but is difficult and potentially dangerous in small children; lack of experience among pediatric radiologists in performing or interpreting the test further hinders its usefulness. A V/Q scan is the preferred test to document a PE in a child (50), but again, requires IV access. Because of its non-invasiveness and fast scan time, a spiral computed tomography scan is often obtained, although the study has not been validated in children (54) and a V/Q scan or MR angiogram needs to follow a negative or equivocal test when suspicion for PE is high.

Thrombotic pediatric stroke is best diagnosed by MRI, with sensitivity increased using perfusion imaging or magnetic resonance venography (MRV)/magnetic resonance arteriography (MRA) (55); while conventional cerebral angiography remains the gold standard, its practical application is limited to specific diagnostic indications (56). CT scans, although fast, fail to detect a significant number of sinovenous thromboses (34). Recently, transfontanelle power Doppler has shown fair, although not equivalent, sensitivity when compared to MRI/MRV for the diagnosis of neotnatal SVT (34). The duration of the MRI/MRV, in particular, and the necessity for the patient to remain relatively motionless means that the child usually requires sedation. The need for sedation to achieve adequate imaging studies in children is nearly universal, and potential morbidity and logistics of sedation (coordinating physicians', nurses' and technicians' schedule with the feeding schedule of an infant) often limit imaging.

Because of advanced equipment, technical support, and extensive experience at most children's centers, echocardiography is an excellent, non-invasive test for right atrial clots. However, there is some evidence that echocardiography may not always be sensitive for the diagnosis of right atrium or inferior vena cava clots and that contrast venography is the preferred diagnostic test for intracardiac clots in this age group (30). There have been no studies comparing echocardiography with cardiac catheterization (33).

Renal ultrasound with Doppler flow is the recommended study for a renal vein or artery thrombosis (29, 31, 32). Clots in this area are most frequent in small, sick neonates with umbilical catheters, so a non-invasive test is ideal.

Laboratory Evaluation

In the approach to the child with thrombosis, it is important to avoid the clinician's usual inclination to find a single etiology for the event. Instead, one must assume that the intersection of multiple risk factors has produced the thrombosis. In most cases, some insult to the endothelium will be present (e.g. indwelling vascular catheter, infectious vasculitis) as well as some dysregulation of coagulation (e.g. sepsis, congenital or acquired coagulation protein abnormality). Most pediatric thrombosis patients should receive a broad investigation for congenital prothrombotic states and acquired prothrombotic risks (Table 1).

For adult patients, an effort has been made to distinguish between laboratory markers that are associated with venous versus arterial thrombotic risk (57, 58). In children, these distinctions are even less clear than in adults. Most prothrombotic factors have been associated in children with events in both the arterial and venous circulation. As an example, it has been advised not to screen for the Leiden mutation in factor V (FVL) and activated protein C resistance (APCR) in adult patients with arterial thrombosis (58, 59). Series of pediatric thromboses, venous and arterial, include children with APCR or FVL in the heterozygote or homozygote state, or in combination with other prothrombotic states (35, 60-66). The data has been recently reviewed (53, 54, 67, 68) suggesting that very selective prothrombotic screens should be avoided,

Table 1 Suggested laboratory evaluation for prothrombotic risk

Coagulation Proteins and Coagulation-based Assays	DNA-based Assays
Protein C	FV G1691A*
Protein S (activity; free and total antigen)	FII G20210A
AT-III	MTHFR C677T^^
Lupus Anticoagulant	Serum-based Assays
Fibrinogen	Antiphopholipid antibodies** (include anticardiolipin^)
Plasminogen	Homocysteine^^
	Lp(a)^
	Total Cholesterol, LDL, HDL, triglycerides

See also (23,36, 45-47, 53, 67).
*Ideally, do APCR in addition, but APCR should not substitute for DNA testing in pediatric patients
^Strongest association with stroke(23). Increased risk with Lp(a) at levels >30 mg/dl (33, 65)
**Especially if pulmonary embolism occurs in apparently well child (116).
^^Preferably fasting homocysteine level; requirement for methionine load prior to testing is not currently established. Independent significance of homozygous MTHFR T/T polymorphism in children remains to be established.

as: 1) compound heterozygote states impart a greater risk of recurrence than single defects (46) (23, 53), and need to be identified and 2) the relative risks associated with different prothrombotic risks are not established in children, and this information needs to be captured, preferably in cooperative registries. A feasible exception may be in children belonging to specific ethnic or racial groups in which the prevalence of specific inherited mutations have been shown to be extremely low (69-72). Due to the racial heterogeneity of the population in the United States, most investigators have not excluded screens for factor V Leiden and prothrombin G20210A mutations, for instance, in children who have experienced thrombosis. Some such exclusions would likely be appropriate for screening large asymptomatic populations, but there are currently no indications for such screening in children.

In addition to the specific thrombophilia evaluation suggested, functional assays of fibrinolytic activity have been described, including the euglobulin clot lysis test and the venous occlusion or tourniquet test (fibrinolysis evaluated by comparative tPA and PAI-1 values before and after a standard venous occlusion) (73, 74). Nevertheless, two prospective adult cohort studies fail to support the utility of these tests for predicting the risk of recurrent thrombosis or as an aid in guiding the length of anticoagulant treatment following a first thrombotic episode 75, 76). Several additional factors confound the usefulness of these tests in children. Chief among these are the lack of standardization of normals throughout childhood (77), the large number of variables that can affect levels of PAI-1 and tPA (including sex, age, obesity, diurnal variation, and variations with serum triglyceride, lipid, and insulin levels) (74, 76, 77), and the technical difficulty of obtaining adequate samples in small children. These assays may have value as research tools or for evaluation of patients suspected of having hemorrhage resulting from too robust fibrinolysis, but do not have predictive value for re-thrombosis and cannot be generally applied in the pediatric thrombosis setting.

It is essential to remember that many abnormal results, with the exception of DNA-based tests, need to be confirmed by repeating at least 3-6 months after the acute thrombotic event. In particular, this approach is required to distinguish transient acquired coagulation abnormalities (e.g. consumption of protein C or S secondary to the thrombotic event) from those congenital or acquired abnormalities that represent an ongoing risk of recurrent thrombosis. The physiologic normals for some values (e.g. protein C, protein S) in the premature and first months of life are so low that moderate acquired loss of these factors can lead to levels difficult to distinguish from congenital deficiency. Testing the parents may help with confirmation of the diagnosis acutely.

Outcomes of Thrombosis in Children

Efforts to validate guidelines for treatment of deep venous thrombosis in adults appropriately target improvements in short-term mortality and morbidity. Prospective evaluation has begun into the primary outcomes of death, pulmonary embolism (PE), and post-thrombotic syndrome (PTS), as well as the incidence and patterns of recurrence following childhood thrombosis. Death following childhood stroke occurs in 9-20% (21, 34, 38, 78) of children of all ages, although this figure represents all-cause mortality in children who generally have underlying illness (e.g. cancer, cardiac diseases, sickle cell anemia). Prospective studies of neonatal thrombosis report 9-18% (27, 29) all-cause mortality, with approximately half of deaths attributable to thrombus. Two registries following VTE in any location (79) or non-CNS VTE (17) each report all-cause mortality of 15-17%, but DVT/PE related mortality of only 2%. The later study specifies that all DVT/PE-related deaths (9/405 patients) were in children with upper venous system CVLs.

The risk of recurrence of childhood thromboembolism is reported to be 21.3% in a selected population followed prospectively in the Childhood Thrombophilia Study Group (CTSG-Germany) (46). The median follow-up was 3.5 years after stopping anticoagulation; 31% of recurrences occurred within the first 12 months off treatment, but 7 years follow-up was required to pick up almost 90% of the events. The longer follow-up likely explains the higher recurrence rate than reported in other recent prospective studies. The Canadian Childhood Thrombophilia Registry (CCTR) reported a recurrence rate of 8.1% at a mean time of 6 months from initial thrombosis (17); 6.5% of children with CVL-related thrombosis had recurrent DVT/PE (26). The Dutch registry found 7% recurrence (18) with follow-up of < 1 year. There was a very important effect of prothrombotic laboratory findings on recurrent thrombosis in this population. Nevertheless, the recurrence rates are much lower in some scenarios, such as SVT and AIS in the neonate (1-5%) (33, 34, 38), and renal vein thrombosis in infants.

The incidence of PE in children, as a primary event or following DVT, is unknown. PE is likely under-recognized in infants, who often have underlying respiratory disease, and under-diagnosed given that the most sensitive diagnostic tests for adults cannot be performed accurately in children. While the CTSG cohort reports (46) 8/109 (7.3%) of children originally presenting with femoral vein thrombosis later have an isolated PE, the risk is doubled if a central line stays in place, or in the presence of cardiac malformation (17).

Conversely, renal vein thrombosis in children is diagnosed increasingly early in children. The mortality rate has fallen to < 5%, especially with institution of anticoagulation in extensive or bilateral thrombosis (29, 31). Renal atrophy, hypertension, and decreased urinary concentrating ability are common, however.

The long-term outcomes of stroke in childhood differ from those in adult stroke in that hemiparesis is less common, seizures are more common, and eventual impairment is difficult to predict from the initial symptoms. Approximately 40% of children with neonatal AIS and 16% of children with neonatal SVT will have moderate to severe neurologic impairments after two years follow-up (35, 37, 64); with stroke onset later in childhood, AIS results in moderate to severe neurologic deficits in > 50%, and SVT in about one quarter (22, 37). Whether anticoagulant therapy can decrease lifelong neurologic impairments in children is among the most pressing questions begging pediatric clinical trials.

A complication that is increasingly recognized in children is the post-thrombotic syndrome (PTS). In the PTS, thrombotic venous obstruction results in distal pressure changes and valvular incompetence, causing chronic venous stasis changes in the extremities. Symptoms progress from swelling to pain, skin breakdown, and loss of function. A recent report from Marzinotto et al. (80) reports PTS in 65% of 40 consecutive children with DVT, classified as mild in 52%, moderate in 13%. It is notable that in this group, radiologic non-resolution at 1 year post-thrombosis approximately tripled the risk of the development of PTS. Peters' group (79) following 37 consecutive children with lower extremity DVTs , found PTS (mostly mild) in 57%, 64%, and 82% of those experiencing DVT as a neonate, child, or adolescent, respectively. In addition, this group found that 11 of the 37 children had at least 1 prothrombotic risk on lab evaluation, and 100% of these children developed PTS versus 50% of children who had negative prothrombotic laboratory evaluation (79). The CCTR, with an average follow-up of 3 years, estimates 12.4% of non-neonatal thrombi result in PTS (17). In this cohort, PTS occurred secondary to lower venous system thrombosis in

Table 2 Suggested anticoagulant/thrombolytic therapy in infants and children

Agent	Dosing		Monitoring	Reversal Agents	Adverse Effects
Anticoagulants					
Standard Heparin (86)	Loading	75 U/kg IV	PTT	Protamine	Hemorrhage
	Maintenance		Anti-Xa level		Osteoprosis
	< 1 year	28 U/kg/hr IV			HIT
	> 1 year	20 U/kg/hr			
LMWH					
Enoxaparin (86, 87)	Treatment		Anti-Xa level	Protamine	Hemorrhage
	< 2 months	1.5 mg/kg q12hr SQ	(4-6 hr after dose)	(incomplete)	HIT (rare)
	> 2 months	1.0 mg/kg q12hr SQ			
	Prophylaxis				
	< 2 months	0.75 mg/kg q12hr SQ			
	> 2 months	0.5 mg/kg q12hr SQ			
Reviparin (86)	Treatment		Anti-Xa level	Protamine	Hemorrhage
	< 5 kg	150 U/kg q12hr SQ	(4-6 hr after dose)	(incomplete)	
	> 5 kg	100 U/kg q12hr SQ			
	Prophylaxis				
	< 5 kg	50 U/kg q12hr SQ			
	> 5 kg	30 U/kg q12hr SQ			
Oral Anticogulant (86, 89)	Initial	0.2 mg/kg qd po (max. 5-10 mg)	INR	Vit K FFP PCC	Hemorrhage
Thrombolytics					
TPA (86, 94, 95, 97)	Systemic		PT, PTT		Hemorrhage
	Load	0.0 – 0.5 mg/kg	fibrinogen		
	Continuous	0.01 – 0.5 mg/kg/hr	platelets		
Streptokinase (86)	Systemic		PT, PTT		Hemorrhage
	Load	2000 U/kg	fibrinogen		Allergic
	Continuous	2000 U/kg/hr	platelets		
Urokinase(86)	Systemic		PT, PTT		Hemorrhage
	Load	4400 U/kg	fibrinogen		
	Continuous	4400 U/kg/hr	platelets		

70% of children. These numbers are likely an underestimate, as PTS may become symptomatic in adults at 5-10 years after thrombosis. Although standardized grading systems for this complication exist for adults (81), the different anatomic distribution of thromboses in children requires new standards, and instruments for scoring presence of PTS in children are not validated. At least two groups in North America are attempting to validate scales (80) (M. Manco-Johnson and North American Pediatric Thrombosis Consortium, Personal Communication).

Cost analyses in adults who have had a single thrombotic event suggest that the thrombosis patient is ten times more likely to have further thrombotic complications than age and sex matched controls and that the costs of such complications are 12 times those that develop in controls (82). Thrombotic complications that occur in a child, prior to attaining normal growth, motor development and adult achievement, may carry a greater cost over the lifetime of a childhood thrombosis survivor. There is reason to hope, however, that morbidity from post-thrombotic syndrome, for instance, may be lower in children, with the upper venous system not as susceptible as the lower system to the effect of gravitational dependence aggravating valvular incompetence. Nevertheless, the perception that children don't experience the same complications as adults may prove false, as appropriate attention and measurement instruments are employed in cooperative study of children who thrombose.

Treatment and Prophylaxis

Therapy may have a single or multiple objectives. Children considered at high risk for thrombosis are often treated prophylactically to prevent such events. Following a thrombotic event, immediate therapy is aimed at restoring blood flow and function, while long-term therapy is used to prevent recurrence or extension of a thrombosis. Therapy for thrombotic events may consist of anticoagulation, thrombolysis or a combination of the two. Few trials have been carried out specifically in children to optimize the use of the available therapeutic agents. Rather, data from adult trials has been extrapolated to cover the pediatric population. With the definition of differences in the hemostatic and fibrinolytic systems of the child versus the adult, some alterations have been necessary.

Anticoagulants

Heparin

The two forms of heparin available to the clinician are standard (or unfractionated) heparin (UH) and low-molecular weight heparin (LMWH). Standard heparin augments the natural actions of antithrombin III to inactivate thrombin, factor Xa and other activated factors, while LMWHs primarily augment ATIII's action on factor Xa. Suggested pediatric dosing regimens for standard heparin and some of the LMWH's are available and shown in Table 2. The higher doses typically required in younger children for either form may be due in part to increased clearance or the lower levels of ATIII in younger children (7).

Adverse effects associated with the use of heparin include hemorrhage, osteoporosis and heparin-induced thrombocytopenia (HIT) (83). A recent retrospective cohort study of the occurrence of HIT in the Pediatric Intensive Care Unit demonstrated an incidence of 2.3%, suggesting the incidence (although not the severity) of childhood HIT

Table 3 Suggested minimum duration of therapy with anticoagulants in children

Event	Minimum Post-Thrombotic Therapy
Venous Thrombosis	
Non-catheter related	3 months, treatment dose
Catheter related	3 months, treatment dose, then prophylaxis dose until catheter removed
Recurrent Venous Thrombosis	
Non-catheter related	3 months, treatment dose, then lifelong prophylaxis
Catheter related	3 months, treatment dose, then prophylaxis dose until catheter removed
Arterial Thrombosis	No evidence-based recommendations for duration in children

may be similar to HIT in adults (84). LMWH has enjoyed an increase in usage due to a number of potential advantages over standard heparin. More stable pharmacodynamics permit more uniform dosing, less frequent monitoring and twice daily dosing. Additionally, studies in adults suggest that LMWH carries less risk for heparin-induced thrombocytopenia (HIT) and osteoporosis (17, 85). Relative contraindications to the use of heparin include significant active bleeding, risk for significant bleeding (e.g. perioperatively, underlying bleeding disorders, severe thrombocytopenia) and a history of HIT.

Standard heparin is typically monitored by prolongation of the partial thromboplastin time (PTT), adjusting doses for a target range of approximately 60-85 seconds or 0.3–0.7 U/mL anti-Xa activity (86). LMWH monitoring is exclusively via anti-Xa levels, with a target range or 0.1–0.4 U/mL for prophylaxis and 0.5–1.0 U/mL for treatment doses (87, 88).

Oral Anticoagulants

Warfarin and other oral anticoagulants (OAs) have been commonly used for long-term anticoagulation in both adults and children. As vitamin K antagonists, OAs interfere with carboxylation of the vitamin K-dependent factors (prothrombin, VII, IX and X) leading to lower plasma activity levels for these factors and a decrease in thrombin-generating potential. OA therapy is monitored via the prolongation of the prothrombin time (PT), using the standardized INR. Target ranges vary with the clinical situation, but are typically an INR of 2-3 for most purposes, and a higher range of 2.5-3.5 for patients with mechanical heart valves. Typically, the ultimate dose per unit body weight is inversely proportional to the patient's age (89).

Adverse effects of OAs include hemorrhage and teratogenesis. Theoretical and animal models have raised concerns over the effect of OAs on osteocalcin and bone mineralization in children. A small study found abnormally low bone mineral density in children with and without bone pain on long-term warfarin therapy (90). This finding needs to be examined in larger studies. The incidence of serious bleeding with long-term use of warfarin in pediatric patients appears to be on the same order as that observed in adults, approximately 1% per year (89). As a teratogen, the use of warfarin in pregnancy or those patients with a significant risk of pregnancy is contraindicated. Other contraindications to the use of warfarin include pregnancy or significant risk of pregnancy and increased risks of bleeding as discussed for the use of heparin.

Several issues make the use of OAs more problematic in children. OAs are available in tablet form and administration may be difficult in smaller children. Variable dietary vitamin K intake in children, relatively low levels of vitamin K-dependent factors in infants and aspects of underlying medical conditions (including concurrent medications) complicate the maintenance of stable therapeutic levels. Frequent monitoring of the INR via venipuncture can be traumatic and technically difficult in children, although the use of whole blood monitors requiring only finger sticks may overcome this obstacle (89, 91).

Thrombolytics

Thrombolytic agents act by converting endogenous plasminogen to plasmin, which then cleaves the fibrin clot. The three thrombolytic agents in use are urokinase (UK), streptokinase (SK) and tissue-plasminogen activator (tPA). Urokinase usage has declined due to recent US FDA warnings over manufacturing deficiencies. Streptokinase carries the risk of significant allergic reaction. Thus, at present tPA is the agent of choice in the pediatric population. As with anticoagulant therapy, the primary adverse effect associated with thrombolytic therapy is bleeding. The reported incidence of major bleeding complications in children associated with thrombolytic therapy varies widely, from 0 to 39% (92-95) A retrospective study found an incidence of < 2% intracranial hemorrhage, with the majority of cases occurring in preterm infants (96). It appears the risk is dose-related and therefore dosing ideally should be with the lowest effective dose. Contraindications to thrombolytic therapy are more extensive than for anticoagulation and include recent internal hemorrhage, GI bleeding or major surgery, thrombocytopenia, the presence of CNS lesions such as CVA within the past year, head trauma, brain surgery or neoplasms. Relative contraindications include bacterial endocarditis, uncontrolled hypertension, acute pancreatitis, active peptic ulceration and pregnancy.

Unfortunately, the large studies required to determine minimal effective dosing have not been performed and a variety of dosing regimens have been used (93, 96-98). While earlier reports described tPA infusion rates of up to ~0.5 mg/kg/h, a recently reported dose-finding experience in twenty children found that rates of 0.01mg/kg/h (for catheter-directed local therapy) to 0.03 mg/kg/h (systemic therapy) were both safe and efficacious (98). A more recent practice has been to include concomitant low-dose heparin, to prevent clot progression and suppress any procoagulant activity of thrombin exposed during clot lysis. This practice does not appear to be associated with an increased incidence of serious bleeding (93, 98).

Indications

An extensive review of the evidence available to support indications for prophylaxis and treatment of thrombotic disease in children has been recently published (86). The more definitive indications are summarized below.

Prophylaxis

Prophylactic anticoagulation may be either primary (prevention of 1st thromboembolism (TE) in high-risk situations) or secondary (prevention of new or recurrent TEs in patients with thrombosis). As the risks for DVT are much lower than in the adult population, indications for primary prophylaxis in the pediatric population are fewer.

Complete (homozygous) deficiency of protein C or S in the newborn period requires immediate and life-long therapy. Typically, these children are managed with infusions of FFP until the diagnosis is made. Thereafter, short-term management is accomplished with FFP infusions for either deficiency; protein C concentrate for PC deficiency; or cryoprecipitate for PS deficiency. OAs are a common and effective choice for long-term management (86, 99, 100). Heterozygous deficiency of PC, PS and other heterozygous congenital thrombophilias are weaker risk factors for thrombosis in childhood, with early thrombotic events starting late in the second decade of life (101-103). There is no evidence to support a recommendation for primary prophylaxis of such children.

Although LMWH and OAs have been demonstrated to reduce CVL-related thromboses in adults, but attempts to conduct similar large-scale trials in children with CVLs have failed (17, 104). At present, there is not sufficient data regarding any prophylactic regimens to make specific recommendations for children with central venous catheters. Arterial catheterization in children (cardiac, umbilical, radial artery) is associated with a high incidence of thrombotic events as well. In contrast to venous catheters, there is sufficient evidence from clinical trials to recommend primary prophylaxis with heparinization in the case of arterial catheterization, as either a pre-procedure bolus for cardiac catheterization or as a continuous infusion when umbilical artery catheters are employed (86).

Thrombolysis

Indications for thrombolytic therapy are not uniform, but more commonly include restoration of catheter patency and dissolution of venous or arterial thrombi that are threatening life, limb viability or normal organ function. A more recent proposal is the use of thrombolytic therapy to reduce the incidence of post-thrombotic syndrome. As discussed above, estimates of the incidence of post-thrombotic syndrome in children have varied from 12 to 74% (17, 105). It has been suggested that the incidence may be decreased with a more rapid dissolution of the clot, with some clinical data in adults supporting this practice (93, 106). The necessary pediatric clinical trials have not been conducted.

Other

Aspirin acts as both an anti-inflammatory and an anti-platelet agent, both effects that may reduce the risk of certain thrombotic events. Aspirin therapy in children with Kawasaki's disease is standard. Prophylactic use in children with Blalock-Tausig shunts has been recommended (86). Jacobs et al. (107), recently reported their surgical team's experience with prophylactic use of aspirin following Fontan procedures, which strongly supports the ongoing multicenter randomized trial of aspirin for this indication. In addition, the use of low-dose aspirin therapy as secondary prophylaxis of ischemic stroke in children has been suggested, but its efficacy has not been demonstrated in the pediatric population (47).

Indications for the use of antithrombin agents, in particular hirudin analogues (hirudin, lepirudin, bivalirudin) and the thrombin active site inhibitor argatroban, are being established in adults. Each of these agents has a short half-life (< 90 min) and there is no antidote to the anticoagulant effect. These agents are useful in the treatment of heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia with thrombosis (HITT) in adults. No evidence-based recommendations for pediatric use are available, although successful use of hirudin for this complication has been reported in at least five children (83, 108). Case reports also suggest danaparoid sodium has efficacy in this scenario, although the latter drug may require higher doses per body weight in children than in adults (83, 109). The use of argatroban for systemic anticoagulation during extracorporeal membrane oxygenation in children has been proposed, but experience in pediatrics is extremely limited (110).

Compression stockings are widely used in the adult population. Their effectiveness as primary prophylaxis for DVT in surgical patients has been demonstrated in multiple studies (111). Additionally, the use of compression stockings following a first DVT appears to reduce the incidence of post-thrombotic syndrome in adults (112). The use of compression stockings has not been investigated in an adequate clinical trial in children. As the cost of compression stockings is not negligible, the incidence of thrombosis in children is low, and compliance will likely be low, their use as primary prophylaxis cannot be recommended. However, the use of compression stockings as a means of preventing post-thrombotic syndrome following DVT warrants investigation.

Perspective

Considerable progress in pediatric thrombosis management has followed an increased awareness that pediatric thrombosis does occur, that historical radiologic and laboratory detection and assumed pediatric norms have been limited, that significant morbidity arises from childhood thromboembolism, and that the incidence of childhood thromboembolism is increasing. The trend in recent years toward cooperative multi-institutional and, recently, international studies has accelerated understanding, for example, of pediatric outcomes (PTS, recurrent thrombosis) and risks (congenital and acquired). The Canadian Childhood Thrombosis Registry, the Canadian Pediatric Ischemic Stroke Registry, the German Childhood Thrombophilia and Childhood Stroke Study Groups, and the Pediatric Coagulation Consortium of the Hemophilia Research Society and the American Society of Pediatric Hematology/Oncology, have laid a framework for badly-needed therapeutic trials to establish treatment for children. These trials need to be designed with an appreciation of childhood hemostatic and pharmacokinetic differences from adults. The burden of capturing significant numbers of pediatric events for these trials is an obstacle that dampens enthusiasm for support from pharmaceutical companies and peer review funding. Nevertheless, this burden needs to be weighed against the cost of poor post-thrombotic outcome and lost potential over the entire lifetime of a child.

Acknowledgements

P.E.M. and G.A.A. are investigators of the Pediatric Coagulation Consortium of the Hemophilia Research Society and the American Society of Pediatric Hematology/Oncology. The authors thank Jack Cornell of Singdog Productions for graphics assistance and Julie Blatt and Stuart Gold for critical input.

References

1. 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. Venous Thromboembolic Complications (VTE) in Children: First Analysis of the Canadian Registry of VTE. Blood 1994; 83: 1251-7.
2. Salzman EW, Hirsh J. The epidemiology, pathogenesis, and natural history of venous thrombosis. In: Coleman RW, Hirsch J, Marder V, Salzman E, eds. Hemostasis and Thrombosis: Basic Principles and Clinical Practices. 3rd ed. Philadelphia: JB Lippincott Co.; 1994. p. 1275-96.
3. Andrew M, Monagle P, Brooker L. Thromboembolic Complications During Infancy and Childhood. Hamilton, B.C.: Decker, Inc; 2000. p.5-46, 120-3, 168-74, 250-3.
4. Reverdiau-Moalic P, Delahousse B, Body G, Bardos P, Leroy J, Gruel Y. Evolution of blood coagulation activators and inhibitors in the healthy human fetus. Blood 1996; 88 (3): 900-6.
5. Mautone A, Giordano P, Montagna M, Quercia M, Altomare M, DeMattia D. Coagulation and fibrinolytic systems in the ill preterm newborn. Acta Paediatrica 1997; 86: 1100-4.
6. Andrew M, Vegh P, Johnston M, Bowker J, Ofosu F, Mitchell L. Maturation of the hemostatic system during childhood. Blood 1992; 80 (8): 1998-2005.
7. Andrew M. Developmental hemostasis: relevance to hemostatic problems during childhood. Seminars in Thrombosis and Hemostasis 1995; 21 (4): 341-56.
8. Andrew M, Mitchell L, Vegh P, Ofosu F. Thrombin regulation in children differs from adults in the absence and presence of heparin. Thromb Haemost 1994; 72 (6): 836-42.
9. Schwarz H, Muntean W, Watzke H, Richter B, Griffin J. Low total protein S antigen but high protein S activity due to decreased c4b-binding protein in neonates. Blood 1988; 71: 562.
10. Nitschmann E, Monagle P, Andrew M. Morphological and biochemical features affecting the antithrombotic properties of the inferior vena cava in adult rabbits and rabbit pups. Pediatric Research 1998; 43: 1-6.
11. Trusen B, Ries M, Zenker M, Rauh M, Beinder E, Keuper H, Harms D. Whole blood clot lysis in newborns and adults after adding different concentrations of recombinant tissue plasminogen activator (rt-PA). Seminars in Thrombosis and Hemostasis 1998; 24: 599-604.
12. Siegbahn A, Ruusuvaara L. Age dependence of blood fibrinolytic components and the effects of low-dose oral contraceptives on coagulation and fibrinolysis in teenagers. Thromb Haemost 1988; 60: 361-4.
13. Michelson A. Platelet function in the newborn. Seminars in Thrombosis and Hemostasis 1998; 24 (6): 507-12.
14. Israels S, Daniels M, McMillan E. Deficient collagen-induced activation in the newborn platelet. Pediatric Research 1990; 27: 337-43.
15. Van Cott EM, Grabowski EF. Vascular hemostasis in flowing blood in children. Seminars in Thrombosis and Hemostasis 1998; 24 (6): 583-90.
16. Grosshaupt B, Muntean W, Sedimayr P. Hyporeactivity of neonatal platelets is not caused by preactivation during birth. Eur J Pediatrics 1997; 56: 944-8.
17. Monagle P, Adams M, Mahoney M, Ali K, Barnard D, Bernstein M, Brisson L, David M, Desai S, Scully M-F, Halton J, Israels S, Jardine L, Leaker M, McCusker P, Silva M, Wu J, Anderson R, Andrew M, Massicotte P. Outcome of pediatric thromboembolic disease: a report from the Canadian Childhood Thrombophilia Registry. Pediatric Research 2000; 47 (6): 763-6.
18. van Ommen C, Heijboer H, Buller H, Hirasing R, Heijmans H, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in the Netherlands. J Pediatrics 2001; 139: 676-81.
19. Gurgey A, Aslan D. Outcome of noncatheter-related thrombosis in children: influence of underlying or coexisting factors. J Pediatric Hematology Oncology 2001; 23 (3): 159-64.
20. David M, Andrew M. Venous thromboembolism complications in children: a critical review of the literature. J Pediatrics 1993; 123: 337-46.
21. Lanthier S, Carmant L, David M, Larbrisseau A, deVeber G. Stroke in children: the coexistence of multiple risk factors predicts poor outcome. Neurology 2000; 54: 371-8.
22. Chabrier S, Husson B, Lasjaunias P, Landrieu P, Tarieu M. Stroke in childhood: outcome and recurrence risk by mechanism in 59 patients. J Child Neurology 1999; 15: 290-4.
23. deVeber G, Monagle P, Chan A, MacGregor D, Curtis R, Lee S, Vegh P, Adams M, Marzinotto V, Leaker M, Massicotte P, Lillicrap D, Andrew M. Prothrombotic disorders in infants and children with cerebral thromboembolism. Arch Neurology 1998; 55: 1539-43.
24. Ganeson V, McShane MA, Liesner R, Cookson J, Hann I, Kirkham FJ. Inherited prothrombotic states and ischaemic stroke in childhood. J Neurology, Neurosurgery and Psychiatry 1998; 65: 508-11.
25. Nuss R, Hays T, Manco-Johnson M. Childhood thrombosis. Pediatrics 1995; 96: 291-4.
26. Massicotte MP, Dix D, Monagle P, Adams M, Andrew M, Program CCT. Central venous catheter related thrombosis in children: Analysis of the Canadian Registry of venous thromboembolic complications. J Pediatrics 1998; 133: 770-6.
27. Schmidt B, Andrew M. Neonatal thrombosis: Report of a prospective Canadian and international registry. Pediatrics 1995; 96 (5): 939-43.
28. Lindblad B, Bergqvist D. Aggressive or conservative treatment in subclavian vein thrombosis. In: Eklof B, Gjores J, Thulesius O, Bergqvist D, eds. Controversies in the management of venous disorders. London: Butterworth and Co.; 1989. p. 141-58.
29. Nowak-Gottl U, von Kries R, Gobel U. Neonatal symptomatic thromboembolism in Germany: two year survey. Arch Diseases in Childhood 1997; 76: F163-F7.
30. Roy M, Turner-Gomes S, Gill G, Mernagh J, Gillie P, Schmidt B. Incidence and diagnosis of neonatal thrombosis associated with umbilical venous catheters. Throm Haemost 1997; 78 (Suppl): 724.
31. Mocan H, Beattie TJ, Murphy AV. Renal venous thrombosis in infancy: long-term follow-up. Pediatric Nephrology 1991; 5: 45-9.
32. Bokenkamp A, von Kries R, Nowak-Gottl U, Gobel U, Hoyer PF. Neonatal renal venous thrombosis in Germany between 1992 and 1994: epidemiology, treatment, and outcome. Eur J Pediatrics 2000; 159: 44-8.
33. Andrew M, Monagle P, deVeber G, Chan A. Thromboembolic disease and antithrombotic therapy in newborns. Hematology (American Society of Hematology Educational Program) 2001: 358-74.
34. deVeber G, Andrew M, Adams C, Bjornson B, Booth F, Buckley D, Camfield CS, David M, Hemphreys P, Langevin P, MacDonald EA, Gillet J, Group CPISS. Cerebral sinovenous thrombosis in children. N Engl J Med 2001; 345(6): 417-23.
35. Golomb M, MacGregor D, Domi T, Armstrong D, McCrindle B, Mayank S, deVeber G. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. Annals of Neurology 2001; 50 (2): 163-8.
36. Gunther G, Junker R, Strater R, Schobess R, Kurnik K, Nowak-Gottl U, Group CSS. Symptomatic ischemic stroke in full-term neonates: Role of acquired and genetic prothrombotic risk factors. Stroke 2000; 31: 2437-41.
37. deVeber GA, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. J Child Neurology 2000; 15 (5): 316-24.
38. Lynch J, Hirtz D, deVeber G, Nelson K. Report of the National Institute of Neurological Disorders and Stroke workshop on perinatal and childhood stroke. Pediatrics 2002; 109 (1): 116-23.
39. Mauz-Korholz C, Junker R, Gobel U, Nowak-Gottl U. Prothrombotic risk factors in children with acute lymphoblastic leukemia treated with delayed E. coli asparaginase (COALL-92 and 97 protocols). Thromb Haemost 2000; 83: 840-3.
40. Wermes C, von Depka Prondzinski M, Lichtinghagen R, Barthels M, Welte K, Sykora K-W. Clinical relevance of gene risk factors for thrombosis in paediatric oncology patients with central venous catheters. Eur J Pediatrics 1999; 15 ([Suppl 3]): S143-S6.

41. Knofler R, Siegert E, Lauterbach I, Taut-Sack H, Siegert G, Gehrisch S, Muller D, Rupprecht E, Kabus M. Clinical importance of prothrombotic risk factors in pediatric patients with malignancy-impact of central venous lines. Eur J Pediatrics 1999; 158 ([Suppl 3]): S147-S50.
42. Glaser DW, Medeiros D, Rollins N, Buchanon GR. Catheter-related thrombosis in children with cancer. J Pediatrics 2001; 138 (2): 255-9.
43. Freed M, Keane J, Rosenthal A. The use of heparinization to prevent arterial thrombosis after percutaneous cardiac catheterization in children. Circulation 1974; 50: 565.
44. Kocis KC, Snider AR, Vermilion RP, Beekman RH. Two-dimensional and doppler ultrasound evaluation of femoral arteries of infants after cardiac catheterization. Am J Cardiology 1995; 75: 642-5.
45. Bonduel M. Prethrombotic disorders in children with arterial stroke and sinovenous thrombosis. Archives of Neurology 1999; 56: 967-71.
46. Nowak-Gottl U, Junker R, Kreuz W, von Eckardstein A, Kosch A, Nohe N, Schobess R, Ehrenforth S, Group CTS. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. Blood 2001; 97 (4): 858-62.
47. Kirkham FJ, Prengler M, Hewes DKM, Ganesan V. Risk factors for arterial ischemic stroke in children. J Child Neurology 2000; 15: 299-307.
48. Askalan R, Laughlin S, Mayank S, Chan A, MacGregor D, Andrew M, Curtis R, Meaney B, deVeber G. Chickenpox and stroke in childhood: a study of frequency and causation. Stroke 2001; 32: 1257-62.
49. Sebire G, Meyer L, Chabrier S. Varicella as a risk factor for cerebral infarction in childhood: a case-control study. Annals of Neurology 1999; 45: 679-80.
50. David M, Manco-Johnson M, Andrew M. Diagnosis and treatment of venous thromboembolism in children and adolescents. On behalf of the Subcommittee on Perinatal Haemostasis of the Scientific and Standardization Committee of the ISTH. Thromb Haemost 1995; 74 (2): 791-2.
51. Male C, Chait P, Ginsberg JS, Hanna K, Andrew M, Halton J, Anderson R, McCusker P, Wu J, Abshire T, Cherrick I, Mahoney D, Mitchell L. Comparison of venography and ultrasound for the diagnosis of asymptomatic deep vein thrombosis in the upper body in children: results of the PARKAA study. Thromb Haemost 2002; 87 (4): 593-8.
52. Mitchell L, Chait P, Ginsberg J, Hanna K, Andrew M. Comparison of venography with ultrasound for the detection of venous thrombosis in the upper body of children. Blood 1999; 94 (Suppl 1): 588a (abstract).
53. Nowak-Gottl U, Kosch A, Schlegel N. Thromboembolism in newborns, infants, and children. Thromb Haemost 2001; 86: 464-74.
54. Warrier I. Thrombotic disorders in infancy and childhood. Pediatric Annals 2001; 30: 558-63.
55. Gadian D, Calamante F, Kirkham F, Bynevelt M, Johnson C, Porter D, Chong W, Prengler M, Connelly A. Diffusion and perfusion magnetic resonance imaging in childhood stroke. J Child Neurology 2000; 15 (5): 279-83.
56. Ganeson V, Savvy LS, Chong WK, Kirkham FJ. Conventional cerebral angiography in children with ischemic stroke. Pediatric Neurology 1999; 20 (1): 38-42.
57. Lane D, Grant P. Role of hemostatic gene polymorphisms in venous and arterial thrombotic disease. Blood 2000; 95 (5): 1517-32.
58. Cushman M, Rosendaal F, Psaty B, Cook E, Valliere J, Kuller L, Tracy R. Factor V Leiden is not a risk for arterial vascular disease in the elderly: results from the Cardiovascular Health Study. Thromb Haemost 1998; 79 (5): 912-5.
59. Bauer K. Update on thrombophilia. Hematology (American Society of Hematology Educational Program) 1999: 231-5.
60. Aschka I, Aumann V, Bergmann F, Budde U, Eberl W, Eckhof-Donovan S, Krey S, Nowak-Gottl U, Schobess R, Sutor A, Wendisch J, Schneppenheim R. Prevalence of factor V Leiden in children with thromboembolism. Eur J Pediatrics 1996; 155: 1009-14.
61. Nowak-Gottl U, Koch H, Aschka I, Kohlhase B, Vielhaber H, Kurlemann G, Oleszcuk-Raschke K, Kehl H, Jurgens H, Schneppenheim R. Resistance to activated protein C (APCR) in children with venous or arterial thromboembolism. Br J Haematology 1996; 92 (4): 992-8.
62. Saxena R, Mohanty S, Jain Y. Activated protein C (APC) resistance in Indian children with thromboembolism. Br J Haematology 1999; 105: 313-20.
63. Zens W, Bodo Z, Plotho J, Streif W, Male C, Bernert G, Rauter L, Ebetsberger G, Kaltenbrunner K, Kurnik P, Lischka A, Paky F, Ploier R, Hofler G, Mannhalter C, Myntean W. Factor V Leiden and prothrombin gene G20210A variant in children with ischemic stroke. Thromb Haemost 1998; 80 (5): 763-6.
64. Mercuri E, Cowan F, Gupte G, Manning R, laffan M, Rutherford M, Edwards AD, Dubowitz L, Roberts I. Prothrombotic disorders and abnormal neurodevelopmental outcome in infants with neonatal cerebral infarction. Pediatrics 2001; 107: 1400-4.
65. Nowak-Gottl U, Strater R, Heinecke A, Junker R, Koch H-G, Schuierer G, von Eckardstein A, Group CSS. Lipoprotein (a) and genetic polymorphisms of clotting factor V, prothrombin, and methylenetetrahydrofolate reductase are risk factors for spontaneous ischemic stroke in childhood. Blood 1999; 94 (11): 3678-82.
66. Kenet G, Sadetzki S, Murad H, Martinowitz U, Rosenberg N, Gitel S, Rechavi G, Inbal A. Factor V Leiden and antiphospholipid antibodies are significant risk factors for ischemic stroke in children. Stroke 2000; 31: 1283-8.
67. Manco-Johnson MJ, Nuss R. Thrombophilia in the infant and child. Advances in Pediatrics 2001; 48: 363-84.
68. Bonduel M, Hepner M, Sciuccati G, Torres AF, Pieroni G, Frontroth JP. Prothrombotic abnormalities in children with venous thromboembolism. J Pediatric Hematology/Oncology 2000; 22 (1): 66-72.
69. Hooper W, Dilley A, Ribiero M, Benson J, Austin H, Silva V, Rawlins P, Wenger N, Evatt B. A racial difference in the prevalence of the Arg506→Gln mutation. Thromb Res 1996; 81: 577-81.
70. Ridker P, Miletich J, Hennekens C, Buring J. Ethnic distribution of factor V in 4047 men and women: implications for venous thromboembolism screening. JAMA 1997; 277 (16): 1305-7.
71. Hessner M, Luhm R, Pearson S, Endean D, Friedman K, Montgomery R. Prevalence of prothrombin G20210A, factor V G1691A (Leiden), and methylenetetrahydrofolate reductase (MTHFR) C677T in seven different populations determined by multiplex allele-specific PCR. Thromb Haemost 1999; 81: 733-8.
72. Ho C, Chau W, Hsu H, Gau J, Chih C. Prevalence of factor V Leiden in the Chinese population. Zhonghua Yi Xue Za Zhi 1999; 62 (12): 875-8.
73. Ens GE. Laboratory Evaluation of Fibrinolysis. In: Stiene-Martin EA, Lotspeich-Steininger CA, Koepke JA, eds. Clinical Hematology: Principles, Procedures, Correlations. 2nd ed: Lippincott; 1998. p. 650-6.
74. Kristensen B, Malm J, Nilsson TK, Hultdin J, Carlberg B, Olsson T. Increased fibrinogen levels and acquired hypofibrinolysis in young adults with ischemic stroke. Stroke 1998; 29: 2261-7.
75. Crowther MA, Roberts J, Roberts R, Johnston M, Stevens P, Skingley P, Patrassi GM, Sartori MT, Hirsh J, Prandoni P, Weitz JI, Gent M, Ginsberg JS. Fibrinolytic variables in patients with recurrent venous thrombosis: a prospective cohort study. Thromb Haemost 2001; 85: 390-4.
76. Schulman S, Wiman B. The significance of hypofibrinolysis for the risk of recurrence of venous thromboembolism. Duration of Anticoagulation (DU-RAC) Trial Study Group. Thromb Haemost 1996; 75 (4): 607-11.
77. Eliasson M, Evrin P-E, Lundblad D, Asplund K, Ranby M. Influence of gender, age and sampling time on plasma fibrinolytic variables and fibrinogen: a population study. Fibrinolysis 1993; 7: 316-23.
78. Keidan I, Shahar E, Barzilay Z, Passwell J, Brand N. Predictors of outcome of stroke in infants and children based on clinical data and radiologic correlates. Acta Paediatrica 1995; 83 (7): 762-5.
79. Peters M. Postthrombotic Syndrome in Children. In: Perinatal/Pediatric Hemostasis Subcommittee SaSC, editor. International Society of Thrombosis and Haemostasis; 2001; Paris, France; 2001.
80. Marzinotto V, Choi M, Chan AKC, Andrew M. Post-thrombotic syndrome in children with previous deep venous thrombosis. Thromb Haemost 2001; 78 (Suppl 1): Abstract OC962.

81. Kistner RL, Eklof B, Masuda EM. Diagnosis of chronic venous disease of the lower extremities: the "CEAP" classification. Mayo Clinic Proceedings 1996; 71: 338-45.
82. Bergqvist D, Jendteg S, Johansen L, Persson U, Odegaard K. Cost of long-term complications of deep venous thrombosis of the lower extremities: An analysis of a defined patient population in Sweden. Annals of Internal Medicine 1997; 126 (6): 454-7.
83. Severin T, Sutor AH. Heparin-induced thrombocytopenia in children. Semin Thromb Hamost 2001; 27 (3): 293-9.
84. Schmugge M, Risch L, Huber A, Benn A, Fischer JE. Heparin-induced thrombocytopenia-associated thrombosis in pediatric intensive care patients. Pediatrics 2002; 109 (1): e10.
85. Warkentin T, Levine M, Hirsh J, Horsewood P, Roberts R, Gent M, Kelton J. Heparin-induced thrombocytopenia in patients with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995; 332 (20): 1330-5.
86. Monagle P, Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. Chest 2001; 119 (1 Suppl): 344S-70S.
87. Punzalan R, Hillery C, Montgomery R, Scott C, Gill J. Low-molecular-weight heparin in thrombotic disease in children and adolescents. J Pediatric Hematology Oncology 2000; 22 (2): 137-42.
88. Dix D, Andrew M, Marzinotto V, Charpentier K, Bridge S, Monagle P, deVeber G, Leaker M, Chan A, Massicotte M. The use of low molecular weight heparin in pediatric patients: a prospective cohort study. J Pediatrics 2000; 136 (4): 439-45.
89. Streif W, Andrew M, Marzinotto V, Massicotte P, Chan AKC, Julian JA, Mitchell L. Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. Blood 1999; 94 (9): 3007-14.
90. Cheung AM, Halton J, Dinyari M, Chan A, Shaughnessy S, Webber C, P. M. Bone mineral density (BMD) in a cohort of children on long term warfarin therapy (> 1 year). Thromb Haemost 2001; 78 (Suppl 1): Abstract OC1729.
91. Marzinotto V, Monagle P, Chan A, Massicotte P, Leaker M, Andrew M. Capillary whole blood monitoring of oral anticoagulants in children in outpatient clinics and the home setting. Pediatric Cardiology 2000; 21: 347-52.
92. Leaker M, Massicotte MP, Brooker LA, Andrew M. Thrombolytic therapy in pediatric patients: a comprehensive review of the literature. Thromb Haemost 1996; 76 (2): 132-4.
93. Manco-Johnson MJ, Nuss R, Hays T, Krupski W, Drose J, Manco-Johnson ML. Combined thrombolytic and anticoagulant therapy for venous thrombosis in children. J Pediatrics 2000; 136 (4): 446-53.
94. Gupta AA, Leaker M, Andrew M, Massicotte P, Liu L, Benson LN, McCrindle BW. Safety and outcomes of thrombolysis with tissue plasminogen activator for treatment of intravascular thrombosis in children. J Pediatrics 2001; 139 (5): 682-8.
95. Hartmann HJ, Hussein A, Trowitzsch E, Becker J, Hennecke KH. Treatment of neonatal thrombus formation with recombinant tissue plasminogen activator: six years experience and review of the literature. Arch Dis Child Fetal Neonatal Ed 2001 2001; 85 (1): F18-22.
96. Zenz W, Arlt F, Sodia S, Berghold A. Intracerebral hemorrhage during fibrinolytic therapy in children: a review of the literature of the last thirty years. Seminars in Thrombosis and Hemostasis 1997; 23 (3): 321-32.
97. Chalmers EA, Gibson BE. Thrombolytic therapy in the management of pediatric thromboembolic disease. Br J Haematology 1999; 104 (1): 14-21.
98. Wang M, Hays T, Nuss R, Gruppo R, Balasa R, Bagatell R, Grabowski E, Valentino L, Tsao-Wu G, Manco-Johnson MJ. Dose finding for tissue plasminogen activator (TPA) thrombolysis in children. Thromb Haemost 2001; Supplement 1: P824 (abstract).
99. Pegelow CH, Ledford M, Young JN, Zilleruelo G. Severe protein S deficiency in a newborn. Pediatrics 1992; 89 (4 part 1): 674-6.
100. Dreyfus M, Magny JF, Bridey F, Schwarz HP, Planche C, Dehan M, Tchernia G. Treatment of homozygous protein C deficiency and neonatal purpura with a purified protein C concentrate. N Engl J Med 1991; 325 (22): 1565-8.
101. Procare G. Comparison of thrombotic risk between 85 homozygotes and 481 heterozygotes carriers of the factor V Leiden mutation: retrospective analysis from the Procare Study. Blood Coagul Fibrinol 2000; 11 (6): 511-8.
102. Martinelli I, Bucciarelli P, Margaglione M, De Stefano V, Castaman G, Mannucci PM. The risk of venous thromboembolism in family member with mutations in the genes of factor V or prothrombin or both. Br J Haematol 2000; 111: 1223-9.
103. Bucciarelli P, Rosendaal FR, Tripodi A, Mannuci PM, De Stefano V, Palareti G, Finazzi G, Baudo F, Quintavalla R, GIRTE (Italian Research Group on Inherited Thrombophilia). Risk of venous thromboembolism and clinical manifestations in carriers of antithrombin, Protein C, Protein S deficiency, or activated protein C resistance: a multicenter collaborative family study. Arteriosclerosis, Thrombosis, and Vascular Biology 1999; 19 (4): 1026-33.
104. Andrew M, Investigators P. A randomized control trial of low molecular weight heparin for the prevention of central venous line-related thrombotic complications in children: the PROTEKT trial. Blood 2000; 96 (11): 492a (Abstract #2116).
105. Choi M, Andrew M. Post-thrombotic syndrome in children with previous deep venous thrombosis. Blood 2000; 96 (11): 654a (abstract #2815).
106. Meissner MH, Manzo RA, Bergelin RO, Markel A, Strandness Jr E. Deep venous insufficiency: the relationship between lysis and subsequent reflux. J Vascular Surgery 1993; 18 (4): 596-608.
107. Jacobs ML, Pourmoghadam KK, Geary EM, Reyes AT, Madan N, McGrath LB, Moore JW. Fontan's operation: Is aspirin enough? Is coumadin too much? Annals of Thoracic Surgery 2002; 73: 64-8.
108. Deitcher SR, Topoulos AP, Bartholomew JR, Kichuk-Chrisant MR. Lepirudin anticoagulation for heparin-induced thrombocytopenia. J Pediatr 2002; 140: 264-6.
109. Ranze O, Ranze P, Magnani HN, Greinacher A. Heparin-induced thrombocytopenia in paediatric patients – a review of the literature and a new case treated with danaparoid sodium. Eur J Pediatr 1999; 158: S130-S3.
110. Kawada T, Kitagawa H, Hoson M, Okada Y, Shiomura J. Clinical application of argatroban as an alternative anticoagulant for extracorporeal circulation. Hematol Oncol Clin North Am 2000; 14 (2): 445-57.
111. Agu O, Hamilton G, Baker D. Graduated compression stockings in the prevention of venous thromboembolism. Br J Surg 1999; 86 (8): 992-1004.
112. Brandjes DPM, Buller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, ten Cate JW. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997; 349: 759-62.
113. Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, Powers P. Development of the human coagulation system in the full-term infant. Blood 1987; 70 (1): 165-72.
114. Hathaway W, Corrigan J. Report of Scientific and Standardization Subcommittee on Neonatal Hemostasis: Normal coagulation data for fetuses and newborn infants. Thromb Haemost 1991; 65 (3): 323-5.
115. Andrew M, Paes B, Johnston M. Development of the hemostatic system in the neonate and young infant. Am J Pediatric Hematology Oncology 1990; 12: 95-104.
116. Nuss R, Chudgar U, Manco-Johnson M. Antiphospholipid antibodies and coagulation regulatory protein abnormalities in children with pulmonary emboli. J Pediatr Hematol Oncol 1997; 19: 202-7.
117. Manco-Johanson MJ, Grabowski EF, Hellgreen M, Kemahli AS, Massicotte MP, Muntean W, Peters M, Nowack-Gottl U. Laboratory testing for thrombophilia in pediatric patients. Thromb Haemost 2002; 88: 155-6.
118. Manco-Johnson MJ, Grabowski EF, Hellgreen M, Kemahli AS, Massicotte MP, Muntean W, Peters M, Schlegel N, Wang M, Nowack-Gottl U. Recommendations for tPA thrombolysis in children. Thromb Haemost 2002; 88: 157-8.

Received March 28, 2002 Accepted after revision August 5, 2002